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REVIEW ARTICLE

How to Use Cytodiagnostic Spleen Puncture

Spleen puncture for cytologic diagnosis has been used since the beginning of the century and Sven Moeschlin s monograph on the method has been available since 1947 but apparently it is still an exclusive method used routinely in very few quarters It has the reputation of being a dangerous intervention and the specimen obtained is usually thought to be unduly difficult to assess These prejudicial ideas of spleen puncture are deeply rooted but in my opinion they are nevertheless fundamentally wrong

Using *fine needles* and a *one hand syringe* the spleen puncture may in reality be regarded as a very safe intervention to be avoided only in conditions of overt hemorrhagic diathesis We have not seen any complications in more than 1000 spleen punctures performed by this method during a 10-year period The secret with this safety may be found in the fact that when the one hand syringe is used both puncture and aspiration can be made in the same fraction of a second the risk of respiratory movement of the spleen is thus avoided and the thin needle (0 7 mm o d) will leave a quite negligible lesion

The bad reputation of spleen puncture may be due to experiences with coarse needles including some time consuming manipulations to obtain a *histologic* specimen Due to the specific structure of spleen tissue such specimens will however rarely be satisfactory enough to justify the use of such risky methods to secure them The *histologic* pictures illustrating this presentation (Figs 1 2 and 3) were obtained from splenectomy specimens! The simple cytologic *smear* obtained by the safe fine needle puncture is instead a rich source of valuable diagnostic information often to be expressed in simple terms if only the exaggerated respect for the spleen as an enigma among organs is overcome

The ordinary hematologist will then realize that the spleen aspirate looks like a blood smear though of course containing also a lot of cells not met with in peripheral blood The problems are analogous with those met with in the bone marrow smear with the important difference however that the cytologic picture is usually less complicated in spleen aspirates than in bone marrow smears and that it may be assessed rather quickly using a scheduled pattern of scrutiny

This presentation is meant to be a simple approach to such a pattern of scrutiny not a catalogue of spleen cytology in health and disease but a guide to the clinical maybe accidental visitor to this exotic field of observation what to expect and what to look for in the fine needle spleen aspirate

The spleen parenchyma consists of two distinct components the white pulp and the red pulp separated by the marginal zone by many authors allotted the important role of immigration port of blood lymphocytes aiming at the spleen parenchyma (Fig 1) It is important to realize that both the white pulp and the red pulp are not only represented but usually even distinctly separated also in smears obtained from a fluid aspirate

It is a good plan to start the scrutiny by looking for the representation of the white pulp small coherent tissue fragments containing numerous lymphocytes firmly aggregated around small precapillary vessels (Fig 4) and usually to be found at the ends of the smears It may be difficult to distinguish individual cells packed together in such tissue fragments fortunately however a track of free cells is usually left behind each fragment during smearing among which it is easy to distinguish some typical elements of lymphatic tissue e g the centrocytes and centroblasts of germinal centers (Fig 5) and the curious phagocytic tingible body cells

The cells of the white pulp do not themselves contribute much to the clinical routine diagnosis but they serve as important landmarks in the







Fig 1 Survey picture of the h stology of normal splenic parenchyma (splenectomy specimen from a case of pancytopenia) *Rp* red pulp *Wp* wh te pulp *GC* germinal center *M*=marginal zone *C* cord of B llroth *S* s nuso d (Glutar aldehyde/osmium tetrox ide Epon embedding *1 μm* section May Grunwald Giemsa ×126)

Fig 2 High power of framed area in Fig 1 mainly mar ginal zone *S* sinus lumen *C* cordal space *Pc* pulp cell *Pl* plasma cell n typ cal site *E* tails of s nus endothelial cells (×567)

Fig 3 Splenectomy specimen from a case of aplastic anem a w th *sl ght* hemolys s Detail from red pulp *S* s nusoid *C* cord *Pc*=pulp cell *Ec* s nus endothelium *Structures marked with X are extra tails of* sinus endothel um cells entering the s nuso d lumen interesting structures of h therto unknown s gnif cance (Histotechn cal data as in Fig 1 ×630)

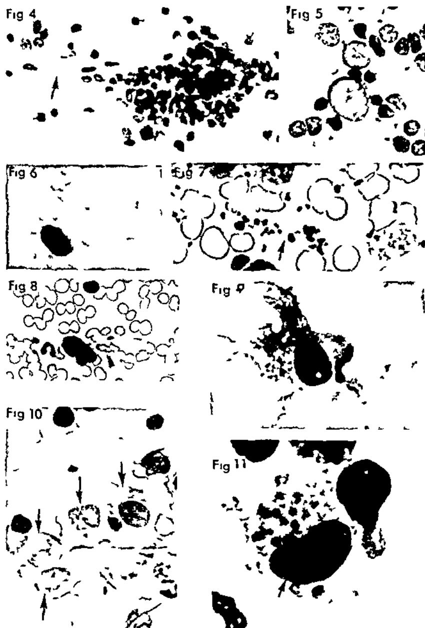


Fig 4 Fragment of white pulp in spleen aspirate from a case of liver cirrhosis Arrow at precapillary vessel (Air-dried smear May-Grunwald-Giemsa ×139)

Fig 5 Centroblasts from white pulp the same case as in Fig 4 (Technical data as in Fig 4 ×278)

Figs 6 7 8 Sinus endothelium cells in spleen aspirates in Fig 8 with multiple tails Specimen in Fig 7 from a case of hemolytic anemia (arrow at tail) Figs 6 and 8 from subnormal spleens (Technical data as in Fig 4 Fig 6 ×348 Fig 7 ×580 Fig 8 ×186)

Figs 9 10 11 Pulp cells (arrows) from spleen aspirates in Fig 9 from the same case as in Fig 3 in Fig 10 from a case of hemolytic anemia in Fig 11 from a case of acute thrombocytopenia (this degree of platelet phago cytosis is an unusual finding) (Technical data as in Fig 4 Fig 9 ×580 Fig 10 ×348 Fig 11 ×580)

tiny if they are few one has to consider previous cytotoxic or corticosteroid treatment or perhaps a massive engorgement of the spleen with blood if they are completely absent, one has to look care fully for the specific cells of the red pulp to exclude the possibility that the object punctured was not a spleen at all

There is one more reason to care for the white pulp fragments at their borders or in their close vicinity one may expect to find the epithelioid cells of *disseminated granulomas* (e g in miliary tuberculosis or sarcoidosis) and the Reed Sternberg cells of Hodgkin s disease (Fig 15) It should be mentioned that some degree of myeloid metaplasia is a standard finding in Hodgkin s disease including more or less numerous megakaryocytes which may be similar to Reed Sternberg cells this is an example of the really difficult diagnosis in spleen aspirates and it should be stressed that spleen puncture can never be used to *exclude* a splenic localization of Hodgkin s disease

Outside the white pulp fragments the smear may be said to represent the red pulp normally a poor representation compared with histology (Figs 6–10) but this fact makes pathologic findings all the more conspicuous Normally it looks like a blood smear with a modest addition of lymphocytes of isma cells of platelet aggregates (Fig 13) and ly of the specific parenchymal cells of red sinus endothelium cells and pulp cells (Figs 11) The double (or multiple) tailed *sinus endo thelium cells* (Figs 6–8) are unique members of the *spleen cytology but often demand some acuity of* observation not to be overlooked the long tails are often poorly visible unless marked by phago cytized matter (Fig 7) The *pulp cells* of Moeschlin the large phagocytic cells of the Billroth cords (Figs 9–12) are very active members of the splenic work shop but often less conspicuous than one might expect Loaded with red cells in hemolytic con ditions with platelets in consumption thrombo cytopenias or with different foreign particles taken up from blood (bacteria!) they will catch the atten tion as diagnostic arguments They are heavily loaded with hemosiderin in hemolysis and hemo siderosis and in different types of metabolic disease they may take a more or less specific appearance as Gaucher cells (Fig 16) Niemann Pick cells or the often Gaucher like cells seen in long standing thrombocytopenia (Fig 17)

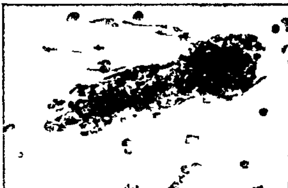
The cytologic picture most often looked for in spleen aspirates and easily detected also by the beginner is *myeloid metaplasia* in myelosclerosis and chronic myeloid leukemia making the red pulp areas look like a bone marrow smear and obscuring the white pulp fragments Myeloid metaplasia of various degrees is a long chapter in splenology I will mention here only the pure red cell metaplasia in some hemolytic anemias and the myeloid meta plasia in different malignant lymphomas including Hodgkin s disease In early stages of myelosclero sis no diagnosis is possible *without a spleen punc* ture

Spleen puncture also contributes essentially to the diagnosis of malignant lymphoma especially in the still poorly known group of lymphomas which apparently start in the spleen I would especially mention the value of spleen aspirates in the cyto logic diagnosis of macroglobulinemia Waldenstrom though admittedly this performance demands considerable experience (Fig 14) Sometimes even a myeloma may be first detected here but usually *the colonization of the spleen by myeloma cells is* a late event in the course of the disease

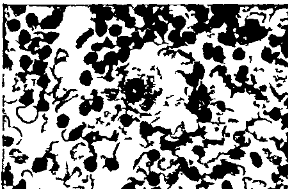
This illustrates the role of the spleen as a bow net placed in the circulation the explanation of sometimes rather surprising findings Cancer cells are now and then seen usually few in numbers and easily overlooked In sclerosing cancer meta stasis to the skeleton *osteoblasts* may be found in the spleen In acute hepatic disease numerous hepatocytes may be present in the spleen aspirate and induce doubts as to the target chosen for punc *ture I have even seen tubular epithelium cells in* spleen aspirates after kidney transplantation (!) Such foreign cells may appear morphologically viable but usually show some signs of degeneration Their presence stirs the imagination regarding the normal sized spleen as a possible source of infor mation in diseases where nobody today would de vote any attention to the spleen

Such confusing findings in spleen aspirates in duce another important conclusion the spleen puncture is not to be compared with an ordinary biopsy *There is no such thing as a specific spleno-*pathy awaiting the spleen biopsy for a final per emptory diagnosis The spleen is a mirror in which various pathologic processes all over the body may be more or less distinctly reflected to the help of an observer who is prepared to pick up the often unexpected piece of information offered by the spleen cells The observer best adapted to

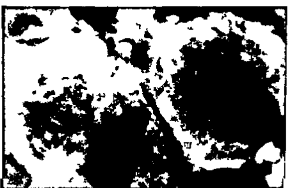












Fg 12 A group of pulp c lls w th typ cal nucle and typ cal cytoplasm c sta n ng (May Grunwald G emsa 1 470)

Fg 13 Sausage l ke agglome ate of pla elets rep esent ng the cast of a B llroth cord—a charac er s c find ng in spleen asp rates (May Grunwald G emsa 794)

Fg 14 A rosette of lymphocytes and small plasma cells a ound a h st ocyte in spl en a p a e from a ca e of Waldens rom s mac oglobu n mia (May G un ald G emsa × 630)

Fg 15 Reed S ernberg cell in spleen asp rate (Ma Grunwald G emsa 794)

Fg 16 Gaucher cells n sp een asp ate (May Grunwald G msa 1 470)

Fg 17 Pseudo-Gaucher cells a type of macrophages some mes consp cuous n spleen asp rates f om cases of consumpt on th ombocytopen a Spleen asp rate f om a case of d opath c th ombocytop n c purpura (May Grunwald-G emsa 2 100)

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Malplacement of Endocardial Pacemaker Electrodes in the middle cardiac vein

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ABSTRACT Endocardial transvenous pacemaker electrodes have been implanted in 246 patients owing to symptomatic bradycardia The electrode was mal placed in the middle cardiac vein in 12 patients All the patients were on stable ventricular pacing at the time of implantation The electrodes were still in function in six patients after 5–96 months (average 55) The electrode was replaced in three patients owing to the occurrence of exit block Three patients died during the period under study Right sided bun dle branch block (RBBB) configuration of paced QRS complexes was observed on the ECG when the elec trode was malplaced in the middle cardiac vein As RBBB only occurs with malplacement, the ECG can be employed to ensure correct positioning of the elec trode

Furman and Schwedel (6) introduced in 1959 the transvenous endocardial implantation technique for permanent pacemaker treatment This technique is preferred (despite displacement of 10–20% of the endocardial implanted electrodes) owing to the lower primary mortality and the longer functioning time of the electrodes (7 13)

The endocardial electrode is introduced through a vein in the neck and sited under fluoroscopic control near the apex of the right ventricle Fluoroscopic examination of the patient using the ante rior–posterior projection will fail to disclose an electrode situated in the middle cardiac vein Such a positioning will often produce ventricular pacing with a low *stimulation threshold*

After transvenous implantation the electrode was malplaced in the coronary sinus or the middle cardiac vein in 26 of 354 patients reported by Paeprer et al (16) Only four of these 26 electrodes functioned satisfactorily for more than one year Meyer and Millar (12) have reported on five patients in whom the elctrode was situated in the coronary sinus or middle cardiac vein of these only one functioned after 14 months of implantation

At times the malplacement of an electrode in the middle coronary vein is first discovered at post mortem examination providing the functioning has been satisfactory (4 9 18)

MATERIAL

A permanent pacemaker has been implanted using a transvenous endocardial electrode in 246 patients during a 10-year period (1964–74) The indication for implanta tion has been either bradycardia owing to atrioventricular block or sinus node dysfunction (11 19) The implanted electrode has been replaced in 45 patients owing to elec trode complications the most frequent reason being dis placement (10)

A unipolar Siemens Elema electrode (EM 588 B) was implanted in 156 patients This is introduced by means of a guide catheter which is removed after positioning of the electrode itself In a further 77 patients a unipolar Siemens *Elema electrode (EM 288 or EM 288 B)* was implanted these are introduced by means of a central stylet Fifty-eight patients had a bipolar Medtronic electrode implanted (Chardach 5818) this is also introduced using a central stylet The implantation was carried out under fluoroscopic control using the anterior–posterior projec tion and with the patient *lying in the supine position* At the same time the 2nd standard ECG lead was registered The criteria for correct electrode positioning have been that the tip of the electrode lay less than 5 cm from the apex of the heart and that stable ventricular pacing with a stimulation threshold of less than or equal to 1 2 V is obtained The patients were controlled at 3 month inter vals after implantation until the impulse generator was *changed for the first time after 2 years*

RESULTS

Of the 291 implanted endocardial electrodes 12 (4 1%) were unintentionally implanted in the mid dle cardiac vein and revealed by a review of the X ray pictures (Table I)

Table I *Data on the 12 patients with malplaced electrodes*

Record no	Sex	Type of electrode	Duration of ventricular pacing (mo)	Clinical observations	ECG	Stimulation threshold (V) Initial	After 2 y
1272	♂	EM 588 B	96	Still in function	RBBB	–	1 8
2836	♂	Chardach 5818	72	Still in function	RBBB	1 0	1 5
3095	♀	EM 588 B	51	Still in function	Synchrone p	0 6	1 0
3851	♀	EM 588 B	4	Exit block	Synchrone p	1 0	–
4260	♂	EM 588 B	55	Still in function	RBBB	0 5	1 5
4390	♂	EM 588 B	0 3	*Ventricular fibrillation*	*RBBB*	*0 7*	–
4425	♂	EM 588 B	41	Dead apoplexy	RBBB	0 8	1 8
4541	♂	EM 588 B	50	Still in function	RBBB	0 8	1 0
5157	♂	EM 588 B	9	Dead	RBBB	0 3	–
5251	♀	EM 588 B	43	Exit block	RBBB	1 2	1 8
6570	♀	EM 288	4	Exit block	RBBB	0 5	–
8178	♀	EM 288 B	5	Still in function	RBBB	1 0	–

Nine of 156 implanted EM 588 B electrodes two of the 77 EM 288 and 288 B electrodes and one of the 58 Chardach 5818 electrodes were implanted in the middle cardiac vein There is no significant difference in the incidence of malplacement of the electrodes between the three electrode types

The stimulation threshold after implantation measured with an external impulse generator (Medtronic 5840) was 0 3–1 2 V (average 0 8) At ›e time of the first replacement of the impulse ˜tor after 2 years the threshold was measured patients and was found to be 1 0–1 8 V erage 1 5) The threshold increase was on an average 0 6 V

The QRS complex brought about by the pacemaker showed right sided bundle branch block (RBBB) configuration in 10 patients (Fig 1) During the period under study two patients had a spontaneous frequency that was more rapid than the basic rhythm of the demand pacemaker

In one patient in whom the electrode sited in the middle cardiac vein produced intermittent exit block after 43 months a unipolar ECG was registered from the electrode in the middle cardiac vein and from a newly implanted electrode in the right ventricle (Fig 2) The two electrodes were *used alternatively as the stimulation electrode* and the registration electrode (3) The time required for the spread of activation from stimulation to registration of intrinsic deflection was in both cases approximately 100 msec

All the 12 patients with the electrode positioned in the middle cardiac vein were on stable ventricular pacing at the time of implantation In six patients the electrodes have functioned 5–96 months (average 55) without any functional error being noted either at the clinical or ECG control Three patients died one 10 days after implantation owing to ventricular fibrillation and one 41 months after implantation from cerebral apoplexy In these two cases the fact that the electrode was situated in the middle cardiac vein was demonstrated at post mortem ex

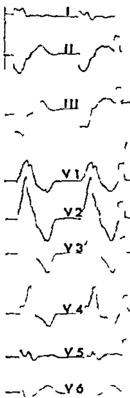


Fig 1 ECG from a 54 year old man treated for 50 months with a pacemaker via an electrode situated in the middle coronary vein

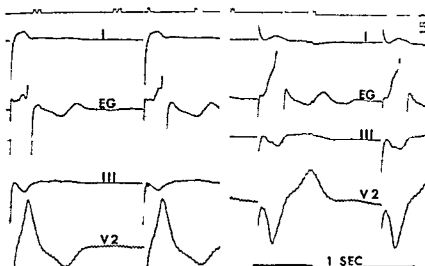


Fig 2 ECG and EG from an 80 year-old woman in connection with the replacement of the electrode *To the left* an EG from an electrode situated in the right ventricle with pacing from an electrode in the middle coronary vein *To the right* an EG from an electrode in the middle coronary vein with pacing from an electrode in the right ventricle

amination (Fig 3) One patient died from general arteriosclerosis 9 months after implantation Post mortem examination was not carried out In three patients the electrode was replaced owing to the occurrence of exit block

The malplacement of the electrode has given rise to diaphragmatic pacing in only two cases In both of these patients the stimulation of the diaphragm ceased a few days after the implantation

DISCUSSION

An electrode situated in the middle cardiac vein produces a similar X ray picture in the anterior–posterior projection to that of an electrode in the apex of the right ventricle (Fig 4) With a lateral projection the electrode can be seen behind the shadow of the heart whereas when the electrode is in the right ventricle it will clearly be seen in the anterior aspect of the heart shadow (9 12 16 18) Campeti et al (2) have studied the X ray projections of the coronary venous system The coronary sinus in the anterior posterior projection runs diagonally upwards to the left while the middle coronary vein goes downwards towards the apex of the heart

The ECG during pacing with the electrode in the apex of the right ventricle shows left sided bundle



Fig 3 A pacemaker electrode (EM 588 B) lying in middle coronary vein



Fig 4 An EM 288 B electrode lying in the middle coronary vein Sufficient function even after 5 months

branch block (LBBB) configuration with left sided axis deviation (3) Only very few reports have appeared on cases where the QRS complex has shown RBBB configuration following stimulation via the endocardium of the right ventricle (15) RBBB configuration is always observed in cases where stimulation occurs from the middle coronary vein (Fig 1) (3 9 12 16 18)

The incidence of malplacement of the electrode in the middle coronary vein in our material is 4 1% Paeprer et al (16) found an incidence of malplacement in the coronary sinus and its branches of 7 3% The size of the orifice of the coronary sinus could be of importance with regard to the incidence Hellerstein and Orbison (8) have studied the size of the orifice of the coronary sinus of 150 hearts from a non selected post mortem material The average diameter of the orifice was 9 6 mm (range 3–19) If the total weight of the heart exceeded 400 g the average diameter was 10 3 mm against 8 8 mm for a normal heart The authors conclude that the difficulty with catheterization of the coronary sinus results from fibro-muscular cords or partial membranes blocking the orifice rather than from variations in the size of the orifice itself All of our 12 patients had a cardiac index of less than 0 5 The incidence of electrode malplacement was independent of the type of electrode used or the implantation technique employed

Exit block occurred in three patients in two of them four months after implantation in one first after 43 months

The stimulation threshold on implantation was below 1 2 V in 11 patients (measurements could not be obtained in one case owing to tachycardia) The increase in the stimulation threshold after 2 years (measured in 6 patients) corresponds to the threshold increase seen with the electrode implanted in the right ventricle (5)

Perforation of the vein or formation of a thrombus around the tip of the electrode can result in an increase in the threshold value thus leading to exit block (14) The tendency to thrombus formation is however reduced owing to the negative charge in the tip of the electrode (17) Intermittent exit block can occur because of movement of the electrode in the vein for example during respiration (1)

Left sided diaphragmatic pacing occurred in two patients Paeprer et al (16) found left sided diaphragmatic pacing in 11 of their 26 patients with electrode positioning in the coronary venous system Only one of 234 patients in our material with a correctly positioned electrode had diaphragmatic pacing Morris et al (13) found pacing of the diaphragm in three of their 51 patients with the electrode placed correctly and no perforation of the myocardium Thus the incidence of diaphragmatic pacing appears to be greater when the electrode is positioned in the coronary venous system than with correct positioning of the electrode within the right ventricle This results from the shorter distance between the tip of the electrode and the diaphragm and phrenic nerve fibres

An optimal technique in order to avoid malplacement of the pacemaker electrode in the middle coronary vein requires the possibility of fluoro-

scopic examination of the patient from several projections The fluoroscope on the other hand will limit the freedom of movement of the operator Routine registration of at least one right sided precordial lead during implantation can however show whether or not the pacemaker impulse via the electrode produces a QRS complex with LBBB configuration or RBBB configuration as a sign that the electrode is implanted in the middle coronary vein This is easily done and gives sufficient assurance that the electrode is correctly positioned

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Table I. *Clinical data on the patients*

Pat. no.	Age (y)	B. wt. (kg)	History: No. of infarctions	History: Location of infarction	History: Complications of latest infarction	Status at selection: Angina pectoris	Status at selection: Validity class (NYHA)	Status at selection: Cardio-thoracic ratio (%)	Reason for stopping exercise at the first test
Drug sequence: lidoflazine→placebo									
1	58	80	1	Inferior	Sinus arrhythmia	No	2	54	General tiredness
4	45	72	1	Posterior	None	No	1	–	Hypotension
5	54	72	2	Inferior	Some left heart failure	Dubious	2	49	ST depression in Z
6	47	79	2	Anterior	None	No	1	45	Dry throat
9	40	83.5	1	Anterior	None	No	2	44	ST depression in X (0.2 mV)
11	47	80	1	Inferior	None	No	2	43	Increase of SBP
12	24	64	1	Inferior	Lung embolism haematothorax	No	2	38	ST depression in Z (0.2 mV)
Drug sequence: placebo→lidoflazine									
2	47	87.5	1	Inferior	None	No	2	46	ST depression in X (0.2 mV)
3	54	76.5	1	Posterior Anterior	III degree AV block+ventricular fibrillation+lung embolism	No	2	–	General tiredness
7	56	79	1	Inferior	None	Yes	2	57	Muscular pain
8	50	73.5	1	Inferior	None	No	1	45	ST depression (0.2 mV)/increase of SBP
10	50	–	2	Inferior	None	No	2	43	ST depression in X
13	25	76.5	1	Anterior	1st day: vasovagal reaction, sinus bradycardia, hypotension, good response to atropine	Dubious	1	47	ST depression in Z/decrease of SBP
	35	80	1	Inferior	Sinus bradycardia	Yes	2	43	ST depression in X (0.2 mV)

Table II. *Haemodynamic data at rest and during exercise*

Pat. no.	At rest: SBP (mmHg) Start	Mo. 3	Mo. 6	DBP (mmHg) Start	Mo. 3	Mo. 6	HR (ECG) (per min) Start	Mo. 3	Mo. 6	During exercise: W_{max} (W) Start	Mo. 3	Mo. 6	SBP at 100 W (mmHg) Start	Mo. 3	Mo.
Sequence: lidoflazine→placebo															
1	160	195	150	90	80	85	72	48	48	110	130	130	170	190	190
4	145	135	–	95	75	–	98	96	–	140	130	–	190	175	–
5	125	110	120	85	75	80	90	90	70	90	100	90	155	160	160
6	130	130	145	90	90	90	74	70	76	100	120	130	180	190	185
9	100	110	105	70	80	75	65	58	59	140	160	180	150	145	150
11	110	130	140	95	80	100	100	99	101	150	160	140	190	160	170
12	140	140	120	100	90	85	80	71	85	130	120	140	200	195	180
Mean except pat. 4	128	136	130	88	82	86	80	72	73	120	132	135	174	173	173
Sequence: placebo→lidoflazine															
2	135	120	120	105	80	90	68	75	62	140	120	120	165	155	150
3	155	135	135	95	95	95	78	93	88	170	150	150	165	180	175
7	140	155	140	95	100	85	66	76	68	150	140	150	180	175	165
8	135	135	120	85	85	70	73	88	64	140	140	140	195	190	185
10	120	135	110	80	80	65	75	65	62	100	100	110	190	190	185
13	125	125	130	95	90	75	75	74	77	150	160	170	170	170	160
14	140	125	140	90	85	90	75	80	65	100	130	130	160	170	170
Mean	136	132	114	92	88	81	72	78	69	136	134	138	175	176	170

Table III *Haemodynamic results*

	Changes during lidoflazine treatment (p)		Lidoflazine vs placebo (p)[a]	Changes during placebo treatment (p)[a]	
At rest					
SBP	No clear changes	n s	n s	No clear changes	n s
DBP	Decrease	0 016	0 023	No clear changes	n s
Differential BP	*Trend to increase*	*0 098*	*n s*	*No clear changes*	*n s*
HR (ECG)	Decrease	0 001	0 0073	Trend to increase	0 076
During exercise					
W_{max}	Increase	0 012	n s	No clear changes	n s
SBP at 100 W	No clear changes	n s	n s	No clear changes	n s
HR at 100 W (ECG)	Decrease	0 002	0 0035	Increase	0 01
HR×SBP at 100 W	Decrease	0 005	<0 0005	Increase	0 006

[a] Wilcoxon matched pairs signed ranks test 1 tailed probability
[b] Kolmogorov Smirnov 2 sample test 1 tailed probability n s =p>0 10

Experimental design and medication

On their entry into the trial the patients were assigned to double blind treatment with either lidoflazine (one 60 mg tablet t i d) or placebo (one tablet t i d) The drugs were supplied as identical tablets each bottle of tablets was identifiable only by its code number referring to the patient and a letter (*A* or *B*) referring to the phase (first or second) of the study After three months there was a cross-over from drug *A* to drug *B* the latter being taken for another three months Each treatment sequence (i e lidoflazine–placebo and placebo–lidoflazine) was assigned to seven patients by an unbiased statistician Lidoflazine was supplied by Janssen Pharmaceutica Beerse Belgium Dr W K Amery contributed to the design of the study

For the entire duration of the trial classical measures regarding diet smoking and hygiene were to be maintained unchanged but normal daily activities including professional work and one hour of adapted physical exercise each day were advised

Other cardiovascular medications were not used except short acting nitrates which were allowed for treatment of anginal attacks only In particular the use of digitalis β blocking agents antianginal drugs antiarrhythmics and diuretics was avoided but anticoagulants were allowed

IR at 100 W (ECG) per min)			HR×SBP at 100 W (mmHg/min)		
tart	Mo 3	Mo 6	Start	Mo 3	Mo 6
120	120	120	20 400	22 800	22 800
140	132	–	26 600	23 100	–
156	138	150	25 420	22 080	26 235
138	138	138	24 840	26 220	25 530
120	114	114	18 000	16 530	17 100
156	144	150	29 640	23 040	25 500
156	150	174	31 200	29 250	31 320
141	134	141	24 916	23 320	24 414
114	118	120	18 810	18 290	18 000
150	145	140	24 750	26 100	24 500
104	176	108	18 720	22 050	17 820
144	*144*	*138*	*28 080*	*27 360*	*25 530*
132	138	132	25 080	26 220	24 420
126	132	125	21 420	22 440	20 000
144	145	128	23 040	24 650	21 760
130	135	127	22 414	24 301	21 432

Assessments

Each patient underwent a full assessment at the time of selection and after three and six months (i e end of first and end of second treatment period respectively)

These assessments consisted of *a*) A careful history with special attention to cardiovascular complaints (such as angina) use of nitroglycerine and/or other medications and validity class according to the NYHA definitions *b*) A physical and laboratory examination for the determination of body weight blood pressure (in recumbent and upright position) cardiac auscultation anomalies and central venous pressure (CVP) Moreover a chest X ray and a resting ECG were obtained and determinations of Hb haematocrit ESR blood cholesterol and triglycerides were made *c*) A bicycle ergometric test of the exercise capacity At selection the assessment was preceded by a submaximal exercise test in order to have the patients adapted to the experimental situation and also to test their intention of cooperating Only the values obtained during the maximal exercise test were taken into account in the analysis of data All patients were exercised under continuous ECG monitoring on a bicycle ergometer The work load was increased by 10 W every minute up to the maximum load tolerated as advised by the WHO (40) Heart rate (HR from the ECG) and systolic blood pressure (SBP) were registered at 50 100 and 150 W (if

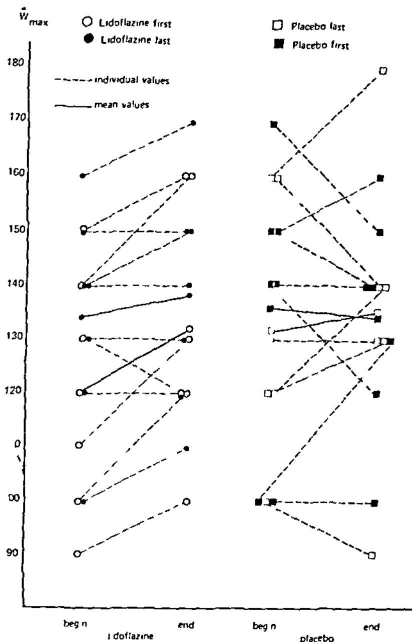


Fig 2 Changes in maximal workload ($\dot{W}_{max}$) during lidoflazine and placebo treatment

reached) and at the maximal work load tolerated ($=\dot{W}_{max}$) The reason for discontinuing exercise was noted

At the end of the trial the investigators compared both treatment periods regarding socio-professional working capacity and possible side-effects Moreover they tried to guess the individual code by comparing HR and SBP at rest as well as at 100 W and $\dot{W}_{max}$ at the end of each treatment phase

RESULTS

Thirteen patients completed the trial One (no 4) dropped out after four months whilst taking place bo because of a recurring infarction

The changes observed during the two treatment sequences (lidoflazine-placebo or the reverse) are similar ($p>0\ 10$ Mann-Whitney U test 2 tailed probability)

Historical data

Since only two patients clearly complained of an gina pectoris at the beginning of the trial no evalua tion was considered in terms of changes in the number of anginal attacks and the use of nitro-glycerine

No difference was found between lidoflazine and placebo regarding NYHA validity class ($p>0\ 10$

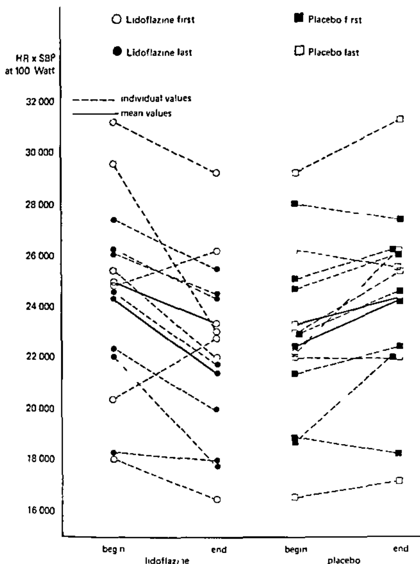


Fig 3 Changes in product of heart rate and systolic blood pressure (*HR×SBP*) at 100 W during lidoflazine and placebo treatment

Wilcoxon matched pairs signed ranks test 1 tailed probability) (36)

Physical examination data at rest and laboratory determinations (Tables II and III)

Body weight SBP CVP cardiothoracic ratio on chest X rays and the various laboratory parameters were not influenced differently by either treatment (p>0 10 same test)

During the lidoflazine period diastolic blood pressure (DBP) and resting HR decreased significantly No similar changes were noted during the placebo period Intertreatment differences in these items were also significant

Bicycle ergometric evaluations (Tables II and III)

At the end of the lidoflazine phase a significant increase in $\dot{W}_{max}$ was noted No similar changes were noted during placebo treatment but inter treatment differences were not significant (Fig 2)

On the other hand a significant decrease was noted during lidoflazine treatment for HR and for the product HR×SBP at 100 W Since these items were found to have increased significantly during the placebo period the intertreatment differences are highly significant in favour of lidoflazine (Fig 3)

Professional activities

Two patients resumed their work during the placebo period and five whilst on lidoflazine In six

patients the work situation remained unchanged during the two treatment periods

Guessing the code

Taking into account five parameters HR and SBP at rest and at 100 W and W_{max} the investigators tried to guess the code of 12 patients (a guess in the remaining patient made no sense since the values of the five items were too similar) and were able to predict the code correctly in 11 This is highly significant ($p<0\ 01$ binomial test)

Side effects and other data

Four patients reported no difference in the incidence of side effects between the two treatment periods five reported more side effects during placebo and four during lidoflazine treatment Possible lidoflazine related side effects were gastric intolerance (one patient) and dizziness (two patients) The most frequently observed adverse experience during placebo treatment was lightheadedness (two patients)

Apart from the double blind medication thirteen patients had used anticoagulants No interaction was observed between lidoflazine and this type of treatment

DISCUSSION

Of special interest in the present study is the increase of W_{max} in post infarction patients during lidoflazine treatment Piessens and De Geest (26) had similar results with comparable methods in a study of patients with angina pectoris Others with different parameters (10 12 25 33 34 35) have reported comparable findings Healthy volunteers also yielded similar results (16 18)

The mechanisms in all these studies are possibly the same The product HR×SBP decreases at submaximal exercise levels after lidoflazine treatment This product may be considered a rough index of the external work of the heart so less strain is put on the heart at the same work load after lidoflazine This in turn might be the reason for reaching a higher W_{max} in several patients

Another point of interest is the decrease in DBP at rest after lidoflazine treatment As far as we know a similar finding has never been reported after lidoflazine treatment in coronary patients Jageneau and Brugmans (18) reported the same phenomenon in untrained volunteers

These results are similar to those of physical training Although none of the patients took part in a training program they were encouraged to be physically active As mentioned in the introduction lidoflazine improves coronary blood supply so patients could have been less limited by their cardiac dysfunction and consequently have been in a better physical condition

Another explanation of the decrease in the HR×SBP product may be that lidoflazine has a direct pharmacological effect both on the heart and on the peripheral circulation At first sight the effects observed in this study appear similar to those of β blocking agents However pharmacologically the drug is quite different *In fact β blocking agents* are not expected to increase W_{max} values in post infarction patients

Although the data indicate a significant effect of lidoflazine on exercise tolerance the actual degree of improvement is rather small In fact it appears to be less than the effect of physical training (27) The practical importance of such a small increase in exercise tolerance seems limited However even a slight decrease in the myocardial oxygen requirement (in terms of a decrease of the HR×SBP product) during work may significantly improve the social abilities of patients It is conceivable that the use of lidoflazine in larger doses and during longer periods may enhance the effects observed in this study

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Renal Function in Normo- and Hypertensive 50-year-old Males

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ABSTRACT Renal function, measured as glomerular filtration rate (GFR) sodium excretion and osmolality after thirst, has been determined in untreated (n=35) and treated (n=22) hypertensives and in a reference group (n=80), all derived from a random population sample of 50-year old men Renal function was related to casual and resting BP and to relative body weight Hypertension was defined as SBP>175 or DBP>115 mmHg on two separate occasions or current antihypertensive treatment Mean GFR was 100±11 7 ml/min in the reference group and significantly lower 94±15 7 ml/min, in the hypertension group In the hypertension group 20% had a reduced GFR, although the standard diagnostic procedure, serum creatinine, demonstrated only 4% Hypertensives with reduced GFR were characterized by higher BP lower urinary sodium excretion, reversed diurnal rhythm of salt and water excretion and a higher relative body weight which was however, explained by the correlation of BP to relative body weight GFR was negatively correlated to DBP at rest and positively correlated to urinary sodium excretion Untreated hypertensives with persistent high BP after rest had lower GFR lower urinary sodium excretion and reversed diurnal rhythm of salt and water excretion indicating high renal resistance The results suggest that subjects with relatively severe hypertension as judged by BP and renal function have an increased renal vascular resistance

Renal blood flow and glomerular filtration rate (GFR) have been shown to be lower in hypertensives than in normotensives In milder forms of hypertension GFR has been normal or only moderately decreased while the decrease in renal blood flow has been more pronounced In more severe hypertension GFR has also been definitely decreased (3 4 6 7 8 9 10 11 16) In a prospective study however Reubi (19) has shown that GFR does not decrease faster with age in most hypertensives than in normotensives

GFR has been shown to decrease with age and to be lower in women than in men (5 22) The urinary concentration capacity has been found to decrease with age (15) Therefore age and sex must be taken into consideration when renal function is investigated in hypertension

This paper presents the results of determination of GFR and sodium excretion in randomly selected groups of normo- and hypertensives of the same age and sex

The aim of the study was to determine 1) the prevalence of impaired renal function in groups of normo- and hypertensive 50-year-old males 2) the characteristics of hypertensives with impaired renal function 3) the relationship between renal function and BP measured casually and at rest

MATERIAL

From a screening examination which was part of a multifactor primary preventive trial (26) in a randomly selected third (n=1122) of the 50-year-old male population in Goteborg Sweden all subjects with previously undiscovered and untreated essential hypertension formed a group of untreated hypertensives (n=35) (Fig 1) The diagnosis of essential hypertension was based on casual BP above 175 systolic and/or 115 mmHg diastolic on two separate occasions two weeks apart and a negative standard diagnostic examination for secondary hypertension (25) Of the untreated hypertension group 18 subjects were classified as belonging to WHO stage 1 13 to stage 2 and 4 to stage 3 (27) All subjects on antihypertensive treatment at the screening examination formed the treated hypertension group (n=22) Fourteen subjects in this group belonged to WHO stage 1 2 subjects to stage 2 and 6 to stage 3 Although the antihypertensive treatment was withdrawn in the treated hypertension group one month prior to the investigation the two hypertension groups are described separately For analysis of characteristics of groups with and without abnormal find

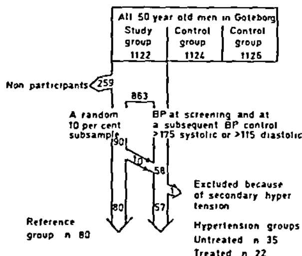


Fig 1 Criteria for selection of the material

ings the groups have been combined to form a single hypertension group A reference group ($n=80$) was obtained from the same age cohort by drawing a 10% subsample at random Ten subjects initially in the refer ence group fulfilled the criteria for hypertension and joined the untreated ($n=5$) or the treated ($n=5$) hyper tension group

The non participation rate in the reference group was 18% (20/110) An analysis of the non-participating group performed later showed no significant differences between s group and those who primarily took part in the screen ..ation with regard to BP heart rate (HR) physi ty smoking habits or prevalence of myocardial stroke diabetes and antihypertensive treat

The reference and hypertension groups were subjected to the same investigations which took place in parallel for the two groups during the spring of 1972 The screening examination was performed in the afternoon between 4 30 and 7 00 p m when the BP is known to be highest (17) The cut-off points for hypertension—175 systolic and/or 115 mmHg diastolic—corresponded to 162 systolic and 101 mmHg diastolic when BP was taken in the morning between 8 and 10 a m (25)

METHODS

Blood pressure was measured at the screening examina tion after a few minutes interview in the seated position using a rubber cuff 12 5 cm broad and 26 cm long con nected to a mercury manometer DBP was recorded as phase 5 i e when the sounds disappeared BP was de termined to the nearest 2 mmHg in order to avoid digital preference BP after 1 hour s rest was measured in the supine position on randomly selected halves of the refer ence and hypertension groups A microphone was placed over the brachial artery The same type of cuff as at screening but with automatic inflation and deflation was used The cuff pressure the Korotkoff sounds and ECG were registered on a Mingograf 81 (Siemens Elema Swe den) The BP was calculated to the nearest 1 mmHg No registrations were obtained for four subjects in the refer ence group

HR at screening and after 1 hour s rest was measured from five consecutive beats on ECG

Height and weight were measured according to Rose and Blackburn (20) except that weight was determined to the nearest 0 5 kg with a lever balance Relative body weight was calculated as weight/height − 100

GFR was determined as the clearance of Cr^{51} EDTA us ng the single injection technique (2) GFR was cor rected to 1 73 m^2 BSA which was calculated according to Isacsson (13) The day to-day variation of GFR determi nations measured in ten subjects was 5% In the analysis of GFR two subjects in the reference group were ex cluded one due to chronic glomerulonephritis verified by biopsy and one for technical reasons In the untreated hypertension group one subject with insulin treated dia betes was excluded from the GFR analysis The fifth per centile in the reference group (80 5 ml/min) was used as the limit between normal and reduced GFR

Determinations of urine volume urinary sodium excre tion and creatinine concentration were performed sepa rately for the day and the night Sodium and creatinine in urine and serum was determined by a Technicon Auto Analyzer To diminish the influence of inadequate urine collection the following criteria for exclusion were set creatinine excretion <1000 mg/24 h or creatinine excre tion ratio day/night >2 1 or night/day >1 5 1 Seven subjects in the reference group one subject in the un treated and three subjects in the treated hypertension group were excluded by these criteria from analysis of variables requiring urine collection

The renal concentration capacity was determined in the hypertensive subjects by measuring urine osmolality (mosmol/kg H_2O) after 13 hours of thirst (12) The osmol ality was determined in urine samples taken at 8 a m The participants had received detailed instructions not to eat or drink after 7 p m the day before the investigation

Chest X-rays of the hypertensive subjects were ex amined by one and the same roentgenologist regarding the presence of a rounded and prominent left ventricle as a sign of left ventricular hypertrophy Cardiac volume was calculated according to Jonsell (14)

Statistical methods

Standard methods were used for calculation of means standard deviations and correlation coefficients The hypothesis of no difference in means between two groups was tested using Student s t test for $n \geq 10$ When the number in a group was <10 the Wilcoxon rank sum test was used The hypothesis of no difference in proportions between two groups was tested by the Fourfold Table Test (21) for $n<60$ and for $n \geq 60$ by the χ^2 test (21) The percentage of expected frequencies <5 was not allowed to exceed 25 and no expected frequencies were allowed to be <1 (18) Differences were considered not significant (n s) for $p>0$ 05 Only 2-sided tests were used

The hypothesis of non-linear correlation between two variables was tested using the correlation coefficient Linear correlations were presupposed for the multiple re gression analysis The independent variables were chosen

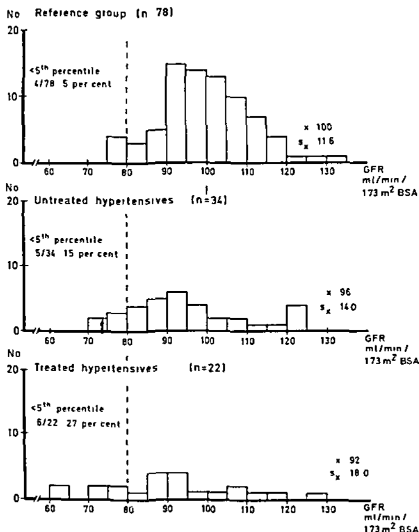


Fig 2 Distributions of GFR and frequency of abnormally low GFR (<80 5 ml/min/1 73 m² BSA)

Table I *Systolic (SBP) and diastolic (DBP) blood pressure and heart rate (HR) before and after one hour s rest in the randomly selected halves of the reference group the untreated and the treated hypertension groups in which phonographic registration of the BP was performed*

	Reference group (n=35)		Untreated hypertensives (n=19)		Treated hyper tensives (n=9)	
	x	s	x	s_x	x	s_x
SBP (mmHg)						
Before rest	144	17 1	197	14 6	167	17 8
After rest	125	14 8	154	23 5	139	15 0
DBP (mmHg)						
Before rest	93	10 0	119	9 2	102	9 9
After rest	78	10 5	96	15 1	86	10 6
HR						
Before rest	75	14 8	84	16 9	73	11 5
After rest	61	10 3	61	8 0	63	5 9

Table II *Urine volume during the day (7 a m –7 p m) and night (7 p m –7 a m) creatinine concentration and urinary sodium excretion in urine samples*

	Urine volume (l)				Creatinine concentration in urine (mg/l)				Urinary sodium excretion (mEq/12 h)			
	Day		Night		Day		Night		Day		Night	
	x	s_x	x	s_x	x	s_x	x	s_x	x	s_x	x	s_x
Reference group (n=74)	0 76	0 29	0 67	0 25	1 270	470	1 290	490	92	32 6	83	32 8
Untreated hypertensives (n=34)	0 73	0 20	0 73	0 25	1 260	490	1 200	480	85	34 8	83	19 2
Treated hypertensives (n=19)	0 71	0 25	0 79	0 33	1 350	430	1 090	570	87	37 6	85	33 9
Hypertensives with GFR >80 5 ml/min/1 73 m² BSA (n=42)	0 74	0 21	0 73	0 19	1 310	440	1 240	500	93*	33 8	87	31 4
Hypertensives with GFR <80 5 ml/min/1 73 m² BSA (n=10)	0 68	0 26	0 84	0 20	1 240	550	920	550	56*	31 1	71	26 8

* p<0 05

on the basis of previously known or biologically probable relationships Whether addition of an independent variable increased the information was judged from the determination coefficient (r^2)

RESULTS

lood pressure and heart rate

lood pressure and heart rate in randomly selected halves of the reference group and the hypertension groups in which BP after rest was measured are presented in Table I In all three groups SBP DBP and HR were significantly lower after than before rest (p<0 01) Untreated hypertensive subjects had significantly higher HR before rest than the reference group (p<0 05) but after rest there was no difference Treated hypertensive subjects had lower SBP and DBP before rest than untreated hypertensive subjects (p<0 01)

Glomerular filtration rate

The results of Cr^{51} EDTA clearance measurements are presented in Fig 2 GFR was 100±11 6 ml/min in the reference group The reference group and the untreated hypertensives did not differ signifi

Table III *Results in the combined hypertension group divided into those with normal GFR and those with reduced GFR (exclusions explain differences in number within the groups)*

	GFR >80 5 ml/min			GFR<80 5 ml/min			Statistical significance (p<)
	n	x	s_x	n	x	s_x	
SBP (mmHg)							
Before rest[a]	29	196	14 2	5	210	13 2	–
After rest[b]	15	149	22 3	3	182	9 0	–
DBP (mmHg)							
Before rest	29	116	8 9	5	127	7 8	–
After rest[b]	15	93	13 5	3	115	6 2	–
Relative body weight	45	1 09	0 12	11	1 18	0 14	0 05
Urinary sodium excretion (mEq/24 h)	42	180	53 0	10	127	46 5	0 01
Urine osmolality (mosmol/kg H_2O)	43	849	195	10	722	189	n s

[a] Only untreated hypertensives
[b] Only untreated hypertensives in the randomly selected half of the group

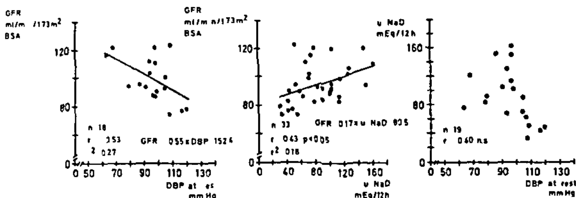


Fig. 3. Relationships between DBP after 1 hour's rest, GFR and urinary sodium excretion during the day.

cantly in GFR but the treated hypertensives had significantly lower GFR than the reference group ($p<0.05$). No difference was found between the two groups of hypertensive subjects. The combined hypertension group (untreated+treated, $\bar{x}=94\pm15.7$) had lower GFR than the reference group ($p<0.05$).

Eleven hypertensive subjects (20%), 5 untreated and 6 treated, had GFR below the 5th percentile in the reference group (80.5 ml/min), which implied a higher prevalence of subjects with GFR below this limit in the combined hypertension group than in the reference group ($p<0.05$). Two subjects, one untreated and one treated hypertensive, had serum creatinine above 1.4 mg/100 ml.

Sodium and water excretion

Urine volume, creatinine concentration and sodium excretion during the day and the night are presented in Table II. No significant differences in mean values were found between the reference group, the untreated and the treated hypertension groups. Hypertensive subjects with reduced GFR had lower urinary sodium excretion during the day than the hypertensives with normal GFR ($p<0.05$). Hypertensive subjects with signs of renal damage (GFR <80.5 ml/min) had a tendency towards smaller urine volume and more concentrated urine during the day than during the night compared to those without such signs. These differences were, however, not statistically significant.

Characteristics of hypertensives with normal and reduced GFR

Forty-five hypertensives, 29 of them untreated, had GFR above 80.5 ml/min. Eleven subjects, 5 of them untreated, had GFR below this limit. Characteristics for these two groups of hypertensive subjects are given in Table III. The group of hypertensives with reduced GFR had higher BP both before and after rest and higher relative body weight ($p<0.05$). These subjects also had lower urinary sodium excretion ($p<0.01$) and a tendency, although not statistically significant, to lower urine osmolality after 13 hours of thirst. There were no differences in heart volume or signs of left ventricular hypertrophy on ECG.

The relationship between BP, GFR and relative body weight

The finding of higher relative body weight in hypertensives with reduced GFR might be caused by systematic underestimation of GFR with higher relative body weight. In the reference group, the linear correlation coefficient (r) between relative body weight and GFR was 0.01, which indicates that this was not the case.

To study the interrelationship between GFR, BP and relative body weight, a trivariate regression analysis of GFR on DBP at rest and relative body weight was performed in the group of untreated hypertensives. The following relationship was found: $GFR=188.44-0.55\times DBP-32.84\times$relative body weight ($r=0.31$). Addition of relative body weight increased r^2 from 0.28 to 0.31, a negligible amount.

The relationship between BP, GFR and urinary sodium excretion

In the reference group there was no significant linear correlation either between BP before and af

Table IV *Results in two parts of the untreated hypertension group one with normalized (n=11) and one with persistently high blood pressure (n=8) after one hour s rest*

	SBP≤165 and DBP ≤100 mmHg		SBP>165 or DBP >100 mmHg		Statistical significance
	$\bar{x}$	$s_{\bar{x}}$	$\bar{x}$	$s_{\bar{x}}$	$(p<)$
SBP before rest (mmHg)	193	16 5	204	9 4	n s
DBP before rest (mmHg)	115	7 8	125	8 7	0 05
Urine volume (l)					
Day	0 83	0 18	0 68	0 21	n s
Night	0 76	0 28	0 73	0 25	n s
Creatinine concentration (mg/l)					
Day	1 190	420	1 380	510	n s
Night	1 120	410	1 290	760	n s
Urinary sodium excretion (mEq/12 h)					
Day	113	31 8	63	23 5	0 05
Night	96	25 8	67	25 7	0 05
Day+night	209	31 3	129	46 3	0 05
GFR (ml/min/1 73 m² BSA)	105	21 4	90	15 9	0 05

ter rest and GFR or between GFR and urinary sodium excretion during the day or between urinary sodium excretion during the day and BP Within the group of untreated hypertensives DBP at rest was negatively correlated to GFR ($r=-0$ 53 $p<0$ 05) Fig 3) Within the same group urinary sodium excretion during the day was positively correlated o GFR ($r=0$ 43 $p<0$ 05) There was no significant correlation between urinary sodium excretion during the day and DBP at rest ($r=-0$ 40)

Renal function in untreated hypertensives with normal and increased resting BP

Table IV gives the results in untreated hyper tensives who had SBP≤165 and DBP≤100 mmHg and for untreated hypertensives with SBP>165 or DBP>100 after 1 hour s rest Mean BP after rest for the former group ($n=11$) was SBP 138±16 9 and DBP 86±12 1 and for the latter group ($n=8$) SBP 175±9 9 and DBP 108±8 0 mmHg Those with persistent high BP after rest ($n=8$) were characterized by significantly higher DBP before rest ($p<0$ 05) than those whose BP was normalized They also had a lower urinary sodium excretion during the day and night and a lower GFR ($p<0$ 05) Although no statistically significant differences were found the results in subjects with persistent high BP after rest suggest that these subjects might have a reversed diurnal rhythm of urine excretion i e a smaller urine volume and a more concentrated urine during the day than during the night compared to those whose BP was normalized after rest

DISCUSSION

The present material has been drawn from the total male population As the subjects in the reference group and the hypertension groups were random samples of the population the results may be generalized to male populations of normo and hypertensive subjects with a similar urban background and a similar age distribution to the present material

As most of the variables investigated are age and sex dependent we have chosen to study normotensive and hypertensive men of the same age The reference group was drawn at random and the hypertension groups were selected so that hypertensives with different severity of the disease had the same chance of being represented Diurnal and seasonal variations in the variables studied should have been ruled out as all examinations were performed at the same time of the day and during the same season To our knowledge no previous quantitative study of renal function in normo and hypertension has used this epidemiological approach

In accordance with previous studies (24 25) the percentage of untreated hypertensives was approximately 60% As BP was lower in the treated hyper

tension group than in the untreated (Table I) only BP of untreated hypertensives have been included in the analysis Our finding of a mean GFR of 100 ml/min in normal 50 year old males is consistent with that of Davies and Shock (5) Reduced GFR was found in 20% of the combined hypertension group while abnormal serum creatinine was found in only 4% Obviously the former method greatly increased the possibility of detecting impairment of renal function

BP measured after one hour s rest was more strongly related to GFR than BP taken without pre vious rest Thus a high BP at rest implies a greater risk of reduced GFR The finding that hyper tensives with reduced GFR had a higher relative body weight than hypertensives with normal GFR was not explained by a direct negative linear corre lation between GFR and relative body weight On the contrary it seemed to be caused mainly by a correlation between BP and relative body weight This finding underlines the necessity of giving hypertension in overweight subjects the same prog nostic and therapeutic importance as in hyperten sives with normal body weight

Our data indicate that severe hypertension i e high BP and renal impairment was accompanied by a low urinary sodium excretion Thus hyper tensives with reduced GFR were characterized by a decrease in urinary sodium excretion apparently out of proportion to the slight renal damage The lower urinary sodium excretion in hypertensives with reduced GFR does not seem to be due to urine collection failure as there was no difference in urine volume between this group and those with normal GFR Assuming steady state conditions the lower urinary sodium excretion in hypertensives with low GFR mirrors a lower salt intake As the hypertension was discovered at the screening ex amination the lower salt intake cannot be due to the hypertensive subjects having been aware of their hypertension and therefore deliberately cut ting their salt intake

A decrease in extracellular volume and/or an in crease in the blood level of angiotension II or aldosterone have been suggested to be the main stimuli to salt intake (23) Thus it is possible that a decrease in urinary sodium excretion leads to a slight increase in extracellular volume and a de crease in plasma renin activity and angiotensin II which in turn depresses salt appetite Whether this mechanism can explain the lower sodium intake in our hypertensives with high resting BP and low GFR will have to be clarified in further studies

Previous hemodynamic studies on hypertensives have shown a reversed diurnal rhythm of salt and water excretion with nocturia and natriuresis due to a lower renal resistance during the night (1) The present results are in accordance with a reversed diurnal rhythm of salt and water excretion in sub jects with severe hypertension The change in di urnal rhythm might very well explain the lower morning urine osmolality in hypertensives with re duced GFR even without the existence of structural tubular damage

Our interpretation of the results is that hyper tensives with established hypertension charac-terized by a high BP even during rest have a higher renal resistance during the day leading to a reduc tion of renal blood flow GFR and sodium excre tion which in turn may lead to a lower salt intake on account of a depressed salt appetite Further studies are needed to clarify the underlying mech anisms and the prognostic implications of these results

ACKNOWLEDGEMENTS

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Systolic Time Intervals in Acute Myocardial Infarction

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ABSTRACT Systolic time intervals (STI) have been measured in 50 individuals without heart disease Electromechanical systole (QS2), left ventricular ejection time (LVET) and preejection period (PEP) but not PEP/LVET, were correlated to heart rate (HR) Regression equations were made and used when correcting STI for HR in two groups of patients a) 51 patients with acute myocardial infarction (AMI) b) 22 patients with chest pains, but no AMI STI was measured on the first 4 days on the 7th day, on the day of discharge and at a control about 60 days later In the AMI group there was a reduction in left ventricular performance from the 1st to the 4th day, and the difference in shortening of LVET was significant ($p<0.001$) while PEP and PEP/LVET increased from the 1st to the 3rd day ($p<0.001$) Between the AMI and the control groups there were significant differences ($p<0.001$) in LVET and PEP/LVET on the 3rd 4th and 7th day, and in PEP on the 3rd and 4th day STI was not found to separate clinical groups with heart failure of different severity The survivors had a lover ($p<0.05$) PEP/LVET on the 1st day than those who died The various localization of the infarction made no difference in STI LVET was found to be strongly correlated ($p<0.001$) to the hydroxybutyric dehydrogenase values

The last decade s progress in care of patients with acute myocardial infarction (AMI) may partly be due to the coronary care units (CCU) The handling of the failing heart in AMI has not been as successful as the handling of the cardiac arrhythmias This may to some degree be explained by our defectiveness in the early diagnosis of heart failure The measurement of systolic time intervals (STI) is a simple and non invasive method for evaluating the left ventricular performance These intervals have shown significant correlation to the angiographically determined ejection fraction and left ventricular end-diastolic volume (7) stroke volume (19) and cardiac output (17) in a wide variety of cardiac diseases

In patients with AMI there is an excellent correlation between left ventricular ejection time (LVET) and stroke volume (6) A lot of investigators have used STI in the evaluation of patients with AMI (1 3 4 6 8 9 10 11 13 14 15 16)

The intention of this study was to investigate 1) the left ventricular performance as expressed by STI in the course of AMI 2) the difference in left ventricular performance between a group of patients with AMI and a group of patients with chest pains but no AMI 3) the variation of STI in patients with heart failure of different severity 4) the prognostic value of STI with regard to heart failure and mortality 5) the STI in infarctions with different localizations and 6) the correlation between STI and the serum enzymes

METHODS AND MEASUREMENTS

Phonocardiogram (PCG) carotid pulse and ECG were simultaneously registered with a Mingograf (Elema Schonander) The carotid pulse curve was obtained by a multipulse transducer (Elettronica Trentina) The transducer was placed over the right carotid artery and was fastened around the neck The PCG was registered with a pick-up (Elema Schonander) placed over the upper part of the sternum

The electromechanical systole (QS2) was measured from the beginning of the QRS complex in the ECG to the second heart sound in the PCG (Fig 1) The LVET was measured from the beginning of the upstroke to the dicrotic notch in the carotid pulse curve (Fig 1) The preejection period (PEP) was calculated as the difference between the QS2 and LVET In this way the pulse transmission time from aorta to the carotid artery was elimi

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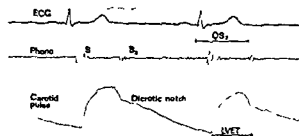


Fig 1 ECG PCG and carotid pulse registered simultaneously Total electromechanical systole (*QS2*) is measured from the beginning of the QRS complex to the second heart sound Left ventricular ejection time (*LVET*) is measured from the beginning of the upstroke to the dicrotic notch of the carotid pulse Preejection period (*PEP*) is calculated as the difference between QS2 and LVET

nated The ratio PEP/LVET was calculated The paper speed was 100 mm/sec QS2 LVET and PEP were measured in msec as the mean of five systoles Each measurement was made to the nearest 0 5 mm (5 msec) The heart rate (HR) was calculated from the R R distance in five systoles and expressed as beats/min

Statistical methods

When comparing the AMI group with the control group the Wilcoxon s two sample test was used In other comparisons the Student s *t* test was used

MATERIAL

The normal group

QS2 and LVET were measured and PEP and PEP/LVET were calculated in 50 individuals (25 women and 25 men) without cardiac disease Their ages ranged from 19 to 66 years (mean 36 3) This group was composed partly of members of the staff partly of patients in the Medical and Neurological Departments

The patient groups

Fifty-one patients with AMI and 22 with chest pains but no AMI admitted to the CCU were examined The diagnosis of AMI was based on a positive history changes in ECG rise and fall in serum glutamic oxaloacetic transaminase (SGOT) and in hydroxybutyric dehydrogenase (HBDH) SGOT was measured on the 1st and 2nd day and HBDH on the 4th day

The AMI group consisted of 33 men and 18 women Seven of them had earlier had episodes of myocardial infarction Their ages ranged from 42 to 82 years (mean 63 6) Nine AMI patients died during the examination period Patients with mitral insufficiency were excluded

In the control group there were 14 men and eight women 17 with ischaemic heart disease but not AMI three with duodenal ulcer one with pneumonia and one with myalgia Their ages ranged from 42 to 73 years (mean 52 5) Both groups were treated in exactly the same way in the CCU

STI was measured on the 1st 2nd 3rd 4th and 7th day The control patients usually were discharged after the 7th day and no further measurements were done in this group In the AMI group STI was measured on the day the patient left the hospital usually on the 21st day No follow up was planned but in 18 patients the STI was measured at a check up two months after discharge

Parallel to the measurement of STI daily clinical examinations were made and the patients were grouped according to a point scale system One point was given for mild congestive failure (rales heard over an area less than half the lung and for each of the medicaments digitalis and furosemide) The use of digitalis in the different clinical groups is shown in Table I Two points were given for severe congestive failure (rales heard over an area more than half the lung pulmonary edema) Three points were given for cardiogenic shock The patients were classified in three groups group A (0 point) group B (1 point) group C (2 3 and 4 points) 2 3 and 4 points were handled together because of few observations At the 2 month control 22 patients were clinically examined

From the regression equations were made tables with the values for QS2 LVET and PEP at different HR QS2 LVET and PEP for each patient were calculated as percentages of the normal values

The localization of the infarction was differentiated in diaphragmatic (15 pats) anteroseptal (8 pats) anterolateral (2 pats) extensive anterior (21 pats) and strictly posterior infarction (1 pat) In four patients the infarction could not be localized

The registration of ECG PCG and carotid pulse curve were made by the nurses at the CCU and at the ECG laboratory In a few registrations we were not able to

Table I *Use of digitalis on each day in the different patient groups*

D=no of patients using digitalis ND=no of not digitalized patients

	Day 1		Day 2		Day 3		Day 4		Day 7		At discharge		At 2 mo control	
	(D)	(ND)	(D)	(ND)	(D)	(ND)	(D)	(ND)	(D)	(ND)	(D)	(ND)	(D)	(ND)
Group A	1	22	0	19	0	16	0	17	1	24	1	25	0	11
Group B	1	9	2	9	2	10	2	9	4	3	4	0	4	0
Group C	3	14	4	13	9	8	8	4	7	1	8	0	3	0
Control	2	20	1	20	2	19	1	16	1	16				

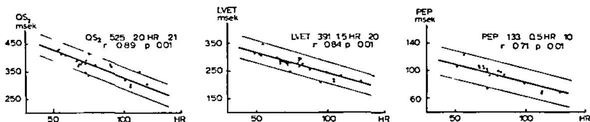


Fig 2 Relation of QS2 LVET and PEP to heart rate in 50 normal subjects ——the regression line —=±2 S D

measure the QS2 and PEP because the second heart sound was difficult to localize and because some of the patients had a left bundle branch block

RESULTS

The normal group

As shown in Fig 2 QS2 LVET and PEP were found to be correlated to the HR The regression equations were as follows

QS2=525−2 0 HR 1 S D ±21 $r=-0$ 89 $p<0$ 001
LVET=391−1 5 HR 1 S D ±20 $r=-0$ 84 $p<$ 0 001
PEP−133−0 5 HR 1 S D ±10 $r=-0$ 71 $p<0$ 001

The ratio PEP/LVET was not correlated to HR (r=0 1) The mean value was 0 35 and 1 S D ±0 05

The patient groups

STI in the course of AMI and in the control group

The results are given in Table II and Fig 3 In the AMI group QS2 and LVET were shortened successively from the 1st to the 4th day and then lengthened to the day of discharge The longest QS2 was found on the 1st day and the longest LVET on the day of discharge The shortest values were on the 4th day In LVET there was a significant difference between the 1st and the 2nd day ($p<0$ 05) between the 4th and the 7th day ($p<0$ 01) and between the 7th day and the day of discharge ($p<0$ 05) The difference in LVET was highly significant between the 1st and the 4th day and between the 4th day and the day of discharge ($p<0$ 001) QS2 was not different from day to day but between the 1st and 4th day there was a significant difference ($p<0$ 01) In the control group there were only minor differences in QS2 and LVET

PEP and PEP/LVET in the AMI group increased from the 1st to the 3rd day and decreased from the 3rd day to the day of discharge The highest values were found on the 3rd day and the lowest at the 2 month control In PEP there was a significant

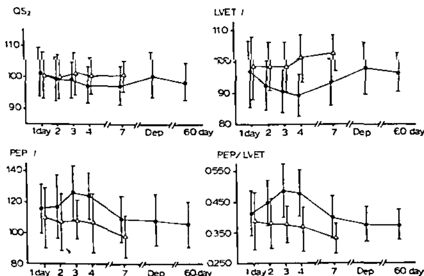


Fig 3 QS2 LVET PEP and PEP/LVET in the groups of AMI patients (●) and controls (Δ) The vertical lines −±1 S D

Table II *QS2 LVET PEP (% of normal values) and PEP/LVET in the AMI group and the control group*

		Day 1	Day 2	Day 3	Day 4	Day 7	At dis charge	At 2 mo control
QS2	AMI							
	x	101 4	99 5	99 2	97 6	97 6	100 8	98 8
	± S D	7 7	6 8	5 7	5 6	6 1	7 0	5 8
	n	48	43	42	39	37	36	17
	Controls							
	x	100 5	100 0	101 0	100 6	101 3		
	± S D	7 0	6 7	6 7	5 8	4 8		
	n	22	21	21	17	17		
		NS	NS	NS	NS	$p<0\ 05$		
LVET	AMI							
	x	96 9	92 4	90 6	89 3	93 5	97 8	96 6
	± S D	9 4	7 7	6 7	6 7	7 3	8 2	6 0
	n	50	47	45	40	40	38	18
	Controls							
	x	98 5	98 6	98 4	101 0	102 7		
	± S D	9 4	7 6	8 0	7 5	5 7		
	n	22	21	21	17	17		
		NS	$p<0\ 01$	$p<0\ 001$	$p<0\ 001$	$p<0\ 001$		
PEP	AMI							
	x	115 8	117 3	126 2	124 1	109 5	109 9	106 4
	± S D	15 8	20 6	17 5	14 9	14 9	16 4	15 1
	n	48	43	42	39	37	36	17
	Controls							
	x	109 9	107 2	108 8	106 6	98 3		
	± S D	19 7	18 5	12 4	19 3	13 4		
	n	22	21	21	17	17		
		NS	NS	$p<0\ 001$	$p<0\ 001$	$p<0\ 05$		
PEP/LVET	AMI							
	x	0 414	0 448	0 487	0 479	0 399	0 379	0 375
	± S D	0 073	0 074	0 087	0 075	0 068	0 056	0 050
	n	48	43	42	39	37	36	17
	Controls							
	x	0 389	0 380	0 378	0 362	0 330		
	± S D	0 093	0 080	0 060	0 073	0 049		
	n	22	21	21	17	17		
		NS	$p<0\ 01$	$p<0\ 001$	$p<0\ 001$	$p<0\ 001$		

difference between the 2nd and the 3rd day ($p<0\ 05$) and the 4th and the 7th day ($p<0\ 001$) In PEP/LVET there was a significant difference be tween the 1st and the 2nd day the 2nd and the 3rd day ($p<0\ 05$) and between the 4th and the 7th day ($p<0\ 001$) *In both PEP and PEP/LVET there were* significant differences between the 1st and the 3rd day ($p<0\ 001$) In the control group PEP and PEP/LVET decreased from the 1st to the 7th day There were only minor differences from day to day

At the 2 month control there were lower values in all four parameters compared to the 1st day and the day of departure

Difference in STI between the AMI group and the control group The results are given in Fig 3 and Table I When comparing QS2 in the AMI group to the QS2 in the control group there was a significant difference only on the 7th day ($p<0\ 05$) In LVET there was a difference on the 2nd ($p<0\ 01$) 3rd 4th and 7th day ($p<0\ 001$) In PEP there was a signifi cant difference on the 3rd 4th ($p<0\ 001$) and on the 7th day ($p<0\ 05$) The ratio PEP/LVET showed a significant difference on the 2nd ($p<0\ 01$) and on the 3rd 4th and 7th day ($p<0\ 001$)

STI and different clinical groups The results are given in Table III Comparing the different clinical

Table III *QS2 LVET PEP and PEP/LVET in the different clinical groups*

		Day 1	Day 2	Day 3	Day 4	Day 7	At discharge	At 2 mo control*
QS2	Group A							
	x	104 3	100 8	99 6	98 5	98 5	102 0	99 9
	± S D	7 0	7 3	5 0	4 5	5 0	8 1	5 2
	n	21	18	16	18	23	25	11
	Group B							
	x	99 8	99 6	100 3	100 5	99 4	101 6	96 8
	± S D	5 0	6 7	3 9	5 1	7 0	6 8	6 8
	n	11	9	13	10	8	5	6
	Group C							
	x	98 8	97 9	97 5	93 4	94 3	95 5	
	± S D	9 1	6 3	7 7	5 5	6 0	6 9	
	n	16	16	13	11	6	6	
LVET	Group A							
	x	101 1	94 0	92 7	91 2	94 8	99 4	98 5
	± S D	7 3	7 5	4 9	4 6	6 2	7 8	5 7
	n	22	19	16	18	24	25	11
	Group B							
	x	95 3	92 5	90 4	89 9	96 1	99 4	93 7
	± S D	5 4	7 2	8 2	4 6	8 1	9 0	5 6
	n	11	10	13	10	9	5	7
	Group C							
	x	92 5	90 6	88 8	85 9	86 6	92 1	
	± S D	11 6	8 3	6 7	8 0	6 3	7 2	
	n	17	18	16	12	8	8	
PEP	Group A							
	x	114 2	121 1	122 8	123 2	108 3	110 5	105 2
	± S D	16 4	15 8	15 0	16 0	15 9	18 7	15 5
	n	21	18	16	18	23	25	11
	Group B							
	x	114 6	119 1	131 6	130 4	107 0	111 4	108 5
	± S D	14 9	15 5	21 1	13 9	8 7	6 3	15 3
	n	11	9	13	10	8	5	6
	Group C							
	x	118 5	119 4	124 8	119 7	118 8	100 7	
	± S D	16 4	17 1	16 5	13 3	17 2	7 8	
	n	16	16	13	11	6	6	
PEP/LVET	Group A							
	x	0 389	0 442	0 455	0 436	0 392	0 385	0 368
	± S D	0 061	0 065	0 058	0 068	0 068	0 065	0 059
	n	21	18	16	18	23	25	11
	Group B							
	x	0 414	0 444	0 510	0 502	0 372	0 378	0 387
	± S D	0 065	0 071	0 118	0 085	0 037	0 034	0 030
	n	11	9	13	10	8	5	6
	Group C							
	x	0 447	0 458	0 486	0 486	0 472	0 370	
	± S D	0 084	0 088	0 077	0 078	0 072	0 025	
	n	16	16	13	11	6	6	

Groups B and C are handled together because there were few observations in each group

groups there were only minor differences between groups A and B and between groups B and C Between groups A and C LVET was significantly different on the 1st day (*p*<0 01) on the 4th day (*p*<0 05) on the 7th day (*p*<0 005) and at discharge (*p*<0 05) QS2 was significantly different on the 1st and the 4th day (*p*<0 05) while PEP/LVET was significantly different on the 1st and on the 7th day (*p*<0 05) PEP was not significantly different on any of the days

STI and the prognosis The results are given in Tables IV and V Comparing the values on the 1st day the survivors had a significantly lower PEP/LVET than those who died (*p*<0 05) PEP and

Table IV *Mean LVET PEP and PEP/LVET on the first day in patients with AMI who died and in patients who survived during their hospital stay*

	Survivors	Deaths	Significance of the difference
LVET			
x	95 9	89 6	
1 S D	15 5	12 2	NS
n	41	9	
PEP			
x	115 2	117 5	
1 S D	16 6	10 4	NS
n	40	8	
PEP/LVET			
x	0 404	0 463	
1 S D	0 072	0 066	$p<0\ 05$
n	40	8	

LVET were not significantly different in the two groups Comparing group A to group B at the 2 month control there were no significant differences in the shortest LVET longest PEP and highest PEP/LVET in the course of each patient

STI and the localization of the infarction The results are given in Table V The patients were grouped according to the localization of the infarction No significant differences in the shortest QS2 and LVET longest PEP and highest PEP/LVET in the course of each patient were found for either localization The numbers of anterolateral and strictly posterior infarction were too small to be tested

STI and the enzyme values (Fig 4) There was a correlation ($r=-0\ 49$ $p<0\ 001$) between the HBDH on the 4th day (x=438 6 U/l 1 S D ±201 2) and the shortest LVET (x=87 2% 1 S D ±5 7) in the course of each patient There was no correlation between HBDH and the longest PEP (x=131 9% 1 S D ±14 3%) and the highest PEP/LVET (x= 0.509 1 S D ±0 073) There was no correlation between the highest SGOT (x=108 U/l 1 S D ± 101 7) and the shortest LVET ($r=-0\ 19$) longest PEP (r=0 02) and highest PEP/LVET (r=0 005)

DISCUSSION

The linear and inverse relation to HR shown for QS2 LVET and PEP in our study is in good agreement with earlier findings (5 18) The ratio PEP/LVET was found to be relatively constant among normal individuals and was minimally influenced by HR The mean value found in our normal group is exactly the same as found earlier by Weissler et al (17)

In our study there was a difference in mean age for the normal group the AMI and the control group Both age and systolic blood pressure are found to influence LVET but only to a minor degree compared to HR (21) With the intention to simplify the calculations we handled men and women together both in the normal group and in the patient groups Earlier findings have shown minor differences in the regression equations for men and women (18)

This study has shown a successive shortening of both QS2 and LVET in the first days after the acute episode of myocardial infarction The maximal shortening was on the 4th day On the 21st day the values were approximately the same as on the 1st day These findings are in agreement with several other studies (1 3 4 6 8 10 11 13 14 15 16) QS2 and especially LVET have been found to be correlated to stroke volume (6) However QS2 and LVET will be shortened by the elevation of catecholamines (1) in the first days after AMI A close correlation between the QS2 and the 24 hour excretion of catecholamines has been shown in one study (12) while others could not confirm this (19) Also drugs with a positive inotropic effect as for example digitalis preparations have been shown to shorten QS2 and LVET (20) A lot of the patients in our study were treated with digitalis even in the first

Table V *Shortest LVET longest PEP and highest PEP/LVET in the course of each patient grouped according of the clinical point score at the 2 month control*

	Group A	Group B	Significance of the difference
LVET			
x	87 4	83 0	
1 S D	4 7	6 8	NS
n	14	9	
PEP			
x	133 5	129 8	
1 S D	12 1	13 6	NS
n	14	9	
PEP/LVET			
x	0 511	0 528	
1 S D	0 061	0 092	NS
n	14	14	

Table VI *Shortest QS2 and LVET longest PEP and highest PEP/LVET in the course of AMI in patients with different localization of the infarction*

No significant differences were found in any of the para meters between any of the groups

	Dia phragmatic infarction	Antero septal infarction	Extensive anterior infarction
QS2			
x	93 0	95 5	95 0
1 S D	7 1	6 9	5 8
n	15	8	20
LVET			
x	85 3	87 9	87 4
1 S D	7 7	7 1	6 0
n	15	8	21
PEP			
x	127 3	135 8	135 9
1 S D	13 8	15 8	13 7
n	15	8	20
PEP/LVET			
x	0 502	0 520	0 526
1 S D	0 080	0 085	0 066
n	15	8	20

days after the acute episode PEP was in this study found to be gradually prolonged in the first three days and decreased towards the 21st day after the acute episode The same variations in PEP are shown by other investigators (3 4 8 16) Reduc tion in stroke volume and cardiac output will tend to prolong PEP (17) The prolongation of PEP and shortening of QS2 and LVET in the first days after the acute episode of myocardial infarction might therefore be an expression of the same matter

However some investigators have shown little or no change in PEP in AMI (1 6 11 13 15) but there was a lengthening from the 1st to the 7th day in a group of patients without left ventricular failure and the longest value on the 3rd day in a group of patients with left ventricular failure (6) Other studies have shown the shortest value on the 1st and 2nd day and the longest on the 5th (10) and the 6th day (15) The discrepancy in the results for PEP may to some degree be caused by the difference in the regression equations used when correcting for HR (5 18)

The subnormal values for PEP found by others are thought to be caused by the raised output of catecholamines in the first days of AMI (15) The difference in the results for PEP and the overlap ping between the AMI and the control group and the different clinical groups may be explained by the shortening of PEP caused by the high cate cholamine output on the one hand and the lengthening of PEP caused by the reduction in stroke volume on the other

The ratio PEP/LVET showed a rise from the 1st to the 3rd day and returned to below the 1st day value on the 7th day This is in agreement with earlier findings (15) Catecholamines and medica ments like digitalis might affect the ratio PEP/LVET to a small degree only because both PEP and LVET are reduced The rise in PEP/LVET in AMI could therefore be a pure expression of the reduction in left ventricular performance Left ventricular ejection fraction (EF) is a hemodynamic measure that correlates well with overall left ven tricular performance and Weissler et al (17) have found a good correlation between EF and PEP/LVET ($r=-0\ 90$)

Our findings have shown a difference in PEP/LVET and LVET from the 2nd to the 7th day between a group of patients with chest pains and a group of patients with AMI These findings are in some contrast to findings in other studies (11 15) The difference between the two groups can be ex plained by the reduction in left ventricular per formance in the sick myocardium compared to the myocardium without infarction

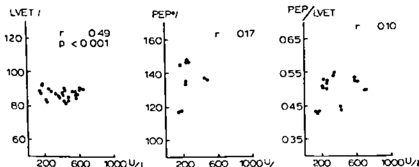


Fig 4 Relation of LVET PEP and PEP/LVET to the HBDH values

In this study STI failed to separate the different clinical groups This may to some degree be caused by the difference in estimating and pointsetting the clinical signs We had to give one point both for mild congestive failure and for digitalis or furosemide therapy Otherwise the medicaments could *hide a failing myocardium because the clinical* signs disappear This is complicating the measuring of STI because failing myocardium and digitalis/furosemide will not influence STI in the same way The lack of correlation between clinical signs and STI may also be explained by the fact that STI is a parameter of left ventricular performance while *the clinical signs are influenced by heterogeneous* factors PEP/LVET was in this study found to be higher on the 1st day in those who died than in the survivors as earlier found by Heikkila et al (10) but we could not confirm the difference in LVET between the same groups of patients

With respect to left ventricular failure measurements of STI during hospitalization could not be used as prognostic indices

The localization of the infarction did not influence the STI which showed almost identical values for anteroseptal and extensive infarction and only slightly lower values for diaphragmatic infarction This should indicate that the localization of the infarction will not influence the left ventricular [illegible] first days after AMI

In our patients with AMI we found a strong [illegible]ation between LVET and HBDH serum levels *Another study has shown good correlation* between QS2 and the LDH level in serum (14) The rise in HBDH has been shown to be in direct relationship to the development of heart failure and cardiogenic shock (2)

Our findings indicate that the reduction in left ventricular performance as expressed by LVET is correlated to the degree of myocardial damage as expressed by the amplitude in serum HBDH rise

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From Medical Department I and the Department of Cardiology Sodersjukhuset Stockholm Sweden

ABSTRACT Antiarrhythmic and hemodynamic effects of i v disopyramide phosphate (1 7 mg/kg b wt over 2 min) have been studied in nine patients, several in various degrees of cardiac decompensation, with sinus rhythm and persistent ventricular ectopic beats (VEBs) In one case with primary cardiomyopathy with >30 VEBs/min disopyramide (DE) abolished the arrhythmia for 30 min, but precipitated brief dyspnoea Other side-effects were tolerable and mainly attributable to anticholinergic effects of the drug DE either abolished or significantly reduced the arrhythmia in all cases For 30 min, only one patient showed VEBs and in three patients no VEBs were seen for three hours Changes in cardiac output and pulmonary artery (PAP) and central aortic pressures were measured in eight patients Negative inotropic effects were indicated in seven by an increased diastolic PAP/stroke volume ratio and in seven by a decreased central aortic $(dp/dt)_{max}$ Patients with high control values for diastolic PAP showed marked reductions in cardiac output, stroke volume and stroke work In predicting myocardial depressant effects of DE the control values for diastolic PAP seemed to be superior to central venous pressure, cardiac index and systolic time intervals Mean arterial pressure measured 5 and 10 min after drug administration showed no significant change, indicating that vasoconstrictor reflexes were well preserved and a pressure level significantly above the control value was reached from the 20th min It is concluded that DE is potent in suppressing VEBs but exerts negative inotropic effects that may be of clinical importance The optimal antiarrhythmic dose is probably lower than that used in the present study

Disopyramide (DE) is a fairly new antiarrhythmic agent that has not yet been investigated extensively The chemical structure (2 phenyl 2(2' pyridyl)-4-diisopropylaminobutyramide) is different from other antiarrhythmic drugs DE possesses anticholinergic effects but no β blocking activity Electrophysiologically the drug exhibits quinidine like properties (4) Orally administered DE has proved effective against arrhythmias following myocardial infarction (2) and also effective in reducing relapses following DC conversion for atrial fibrillation (7) Oral DE significantly reduced the number of ventricular ectopic beats (VEBs) in a long term study (18) The i v route of administration has been used in only a few investigations 1–2 mg/kg b wt was given to patients over 1–5 min in an earlier study (6) In an electrophysiological study the same dose was injected over 5–10 min without any serious side-effects (8)

The present investigation was undertaken to study hemodynamic and electrocardiographic effects following i v administration to patients with ventricular arrhythmias in whom antiarrhythmic treatment was indicated with the exception of one case other drugs had been inefficient or associated with definite side effects

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Six men and three women (mean age 62 years) were studied Individual and clinical data are given in Table I Five patients had had myocardial infarction All were in sinus rhythm and showed a varying number of VEBs Diagnosis of a VEB was based on subjective criteria using prematurity aberrancy and increase in QRS width Patients 2 and 5 had episodes of ventricular tachycardia as defined by at least four VEBs in sequence with a frequency higher than 100/min One of these (no 2) needed repeated DC shock treatment on the day before the study This patient died six weeks after the investigation autopsy showing an old ruptured aneurysm of the right coronary artery and an intramyocardial hematoma

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Disopyramide (DE) is a fairly new antiarrhythmic agent that has not yet been investigated extensively The chemical structure (2 phenyl 2(2' pyridyl)-4-diisopropylaminobutyramide) is different from other antiarrhythmic drugs DE possesses anticholinergic effects but no β blocking activity Electrophysiologically the drug exhibits quinidine like properties (4) Orally administered DE has proved effective against arrhythmias following myocardial infarction (2) and also effective in reducing relapses following DC conversion for atrial fibrillation (7) Oral DE significantly reduced the number of ventricular ectopic beats (VEBs) in a long term study (18) The i v route of administration has been used in only a few investigations 1–2 mg/kg b wt was given to patients over 1–5 min in an earlier study (6) In an electrophysiological study the same dose was injected over 5–10 min without any serious side-effects (8)

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Table I *Some anthropometric clinical and laboratory data for the nine patients studied*

Pat no	Symbol	Sex	Age (y)	Weight (kg)	BSA (m²)	Clinical diagnosis	Drug therapy	Serum creatinine (mg/100 ml)
1	○	♀	75	57	1 61	Hypertension + paroxysmal atrial tachycardia		0 8
2	●	♂	54	70	1 80	Coronary arteriosclerosis + coronary artery aneurysm	Practolol and lidocain stopped a few hours before study	0 8
3	□	♂	67	68	1 78	Myocardial infarction (2 years ago) + diabetes	Furosemide 20 mg/d	1 0
4	■	♀	67	68	1 67	Coronary arteriosclerosis	Furosemide 40 mg/d	0 7
5	△	♀	34	61	1 77	Cardiomyopathy	Digoxin 0 25 furosemide 80, verapamil 240 diazepam 6 mg/d potassium chloride 4 5 g/d	1 1
6	▲	♂	65	87	2 11	Myocardial infarction (14 years ago) + angina pectoris		1 2
7	▽	♂	64	84	1 99	Myocardial infarction (7 years ago) + angina pectoris	Digoxin 0 25 furosemide 240 mg/d potassium chloride 6 g/d	0 8
8	▼	♀	66	61	1 59	Angina pectoris		0 9
9	◆	♂	67	68	1 78	Myocardial infarction 3 times (latest 4 years ago)	Digoxin 0 5 mg/d and furosemide 80 mg/d since day before study Lidocain stopped 2 hours before injection of DE	1 6

Antiarrhythmic treatment had been given to all patients In five cases (nos 1 2 3 8 9) lidocaine had been inefficient in controlling the arrhythmia Quinidine treatment had been discontinued due to inefficacy (no 6) severe diarrhoea (no 5) and nausea (no 4) Patients 3 and 5 had subjectively troublesome ectopic beats and had previously received short term oral DE without serious side effects and with a satisfactory antiarrhythmic response Fre nt supraventricular ectopic beats in addition to VEBs seen in patients 1 6 8 and 9 utine laboratory check up of Hb and serum electro- on the day of the study revealed no abnormalities and erum creatinine values prior to the investigation are shown in Table I as well as concurrent drug therapy The patients were carefully informed about the procedure and had all consented to take part in the study Disopyramide (*Rythmodan*®) was supplied by Roussel Lab Ltd England

METHODS

All patients were studied in the supine position Central venous pressure (CVP) was measured through a teflon catheter inserted into the right subclavian vein Through this tube a fine polyethylene catheter (PE 60) was allowed to float into the pulmonary artery for pressure recordings The position of the tip of this catheter was determined by observation of the pressure curve A teflon catheter (length 1 20 m o d 1 0 mm) was placed in the ascending aorta under X-ray observation The reference point for zero pressure was taken at the mid thoracic level ECG was monitored on an oscilloscope and also recorded continuously on a paper chart at a speed of 10 mm/sec The ECG recording started 10–60 min before the injection and lasted for 3 hours after the administration of DE which was given in a dose of 1 7 mg/kg b wt (3 9 mmol/kg) over a 2 minute period Heart rate (HR) ECG and pressure values were all displayed on UV film (ABEM Ultralette) and these data were also stored on a multichannel tape for computer analysis

The above variables were recorded continuously for 5 min before to 10 min after the start of the injection and thereafter intermittently Cardiac output (Q) was determined in duplicate 5 min before and 10 30 and 180 min after the injection using the dye dilution technique with a Beckman cardiodensitometer Blood required for the dye curves was reinfused into the superior vena cava The maximal derivative of the aortic pressure curve $(dp/dt)_{max}$ and the systolic time intervals were computed 5 min before at the start of and 5 10 20 30 60 120 and 180 min after the injection Pre-ejection period (PEP) was computed from the aortic pressure curve and the ECG Left ventricular ejection time (LVET) also obtained from the aortic pressure curve was corrected for HR by the formula devised by Weissler et al (19) Cardiac index (CI) was calculated from the expression $\dot{Q} \times (BSA)^{-1}$ and stroke index (SI) from the expression $CI \times HR^{-1}$ Total peripheral vascular resistance index (PVRI) was calculated from the formula (mean aortic pressure−CVP)×CI^{-1} Left ventricular stroke work index (SWI) was obtained from the formula (mean aortic pressure–pulmonary artery diastolic pressure)×SI

All hemodynamic results are based on computer derived data as averages from 10–70 normal beats From the tape recordings a 50 cm strip of the ECG was extracted at a speed of 50 mm/sec and analysed for PQ QRS and QT times which are presented as means of five measurements on each strip QT time was not corrected for HR Blood gas tension and acid–base values were determined with gas and pH-electrodes (Radiometer BMS 3) from arterial blood samples taken 10 min before and 30 min after the injection Blood samples for analysis of serum DE con

Table II *Hemodynamic effects of i v disopyramide in eight patients with ventricular arrhythmia*

HR heart rate PEP=pre eject on period LVET left ventricular eject on t me CI=card ac index SI stroke index PVRI peripheral vascular resistance index SWI stroke work index S systol c D diastol c M mean CV central venous

Pat no	Time (min after inj)	HR (min)	Pressures (mmHg) Aorta S	D	M	Pulm artery S	D	M	CV	$(dp/dt)_m$ Aorta (mmHg× ms)	PEP (ms)	PEP/LVET	CI (l× m n m ²)	SI × (ml× m ²)	PVRI (mmHg× m n× m²×l)	SWI (J×m ²)
1	5	93	143	69	98	19	8	14	5	0 94	89	0 199	1 9	[illegible]1	38 8	0 30
	0	9[illegible]	145	65	98	21	7	14	5	1 14	80	0 177				
	5	85	135	69	96	21	14	17	7	0 67	1[illegible]8	0 306				
	10	87	147	72	103	26	15	20	8	0 75	112	0 264	1 7	19	45 6	0 [illegible]7
	20	81			96		9		5	0 89	108	0 [illegible]56				
	30	84	148	68	100	18	9	13	5	0 71	105	0 247	1 6	19	47 [illegible]	0 [illegible]8
	60	76	146	64	96	17	8	12	4	0 71	105	0 [illegible]55				
	120	77	166	70	108	20	8	14	5	0 80	95	0 217				
	180	96	154	68	104	19	9	14	5	0 83	89	0 194	1 8	19	44 0	0 [illegible]9
2	5	91	95	70	81	3[illegible]	9	21	6	0 89	94	0 258	[illegible] 8	31	[illegible] 4	0 33
	0	93	104	76	88	29	12	20	5	0 76	10	0 220				
	5	88	98	76	87	33	[illegible]0	26	13	0 47	1[illegible]8	0 313				
	10	85	98	72	84	29	16	22	9	0 4[illegible]	1[illegible]9	0 320	[illegible] 9	34	20 6	0 35
	20	83	109	78	91	26	13	19	5	0 5[illegible]	1[illegible]8	0 305				
	30	86	119	83	98	28	15	21	7	0 5[illegible]	125	0 311	[illegible] 8	33	[illegible]5 8	0 40
	60	86	118	8[illegible]	97	30	14	21	5	0 51	114	0 [illegible]74				
	120	86	104	76	89	23	12	16	4	0 75	96	0 24[illegible]				
	180	81	115	82	96	13	10	11	5	0 69	83	0 208	3 1	38	[illegible]3 4	0 47
3	5	119	145	81	111	56	26	41	4	1 51	89	0 199	3 5	30	[illegible]4 9	0 38
	0	110	148	89	118	50	30	36	4	1 [illegible]7	91	0 194				
	5	129	139	98	118	44	30	35	10	0 86	1[illegible]8	0 30[illegible]				
	10	125	145	97	120	57	35	44	9	1 0[illegible]	112	0 261	[illegible] 5	20	35 [illegible]	0 [illegible]6
	20	100	150	96	12[illegible]	58	32	42	6	1 23	99	0 [illegible]46				
	30	112	146	92	117	52	27	36	4	1 34	99	0 2[illegible]6	3 0	27	[illegible]9 9	0 37
	60	110	145	89	115	41	31	38	4	1 [illegible]7	97	0 [illegible]				
	120	110	145	87	115	47	27	35	4	0 89	94	0 [illegible]14				
	180	115	146	94	119	53	30	40	5	1 9	96	0 [illegible]4	[illegible]7	[illegible]3	33 4	0 3[illegible]
4	5	66	136	69	97	3[illegible]	12	0	5	0 95	94	0 2[illegible]3	[illegible] 6	38	[illegible]9 [illegible]	0 53
	0	69	143	73	10[illegible]	35	15	23	6	0 98	90	0 [illegible]05				
	5	6[illegible]	148	79	106	30	13	[illegible]0	6	0 70	135	0 33[illegible]				
	10	60	143	74	101	31	14	21	6	0 59	1[illegible]7	0 306	[illegible]	37	34 3	0 51
	20	63	158	79	110	31	13	20	5	0 74	109	0 [illegible]59				
	30	63	154	76	107	33	13	21	6	0-80	10[illegible]	0 [illegible]6	[illegible] 7	43	30 0	0 65
	60	63	167	80	114	33	14	2[illegible]	6	0 84	10[illegible]	0 [illegible]35				
	120	71	143	77	105	34	14	22	5	1 03	9[illegible]	0 [illegible]08				
	180	71	152	79	109	33	13	21	5	0 90	89	0 [illegible]03	[illegible] 7	38	30 9	0 57
6	5	78	138	84	107	47	23	32	4	0 81	156	0 374	1 9	[illegible]4	44 4	0 3[illegible]
	0	82	146	89	112	48	25	34	4	0 88	160	0 369				
	5	109	116	93	103	40	29	33	8	0 44	198	0 491				
	10	107	116	90	101	43	30	34	8	0 48	19[illegible]	0 430	1 5	14	50 9	0 14
	20	100	139	98	115	51	31	39	7	0 57	167	0 4[illegible]7				
	30	97	129	90	107	52	3[illegible]	38	9	0 55	16[illegible]	0 409	1 7	17	45 9	0 [illegible]0
	60	84	156	94	118	51	27	37	5	1 06	151	0 370				
	1[illegible]0	93	164	101	126	49	31	39	3	0 98	160	0 395				
	180	88	153	9[illegible]	117	46	24	33	5	1 00	151	0 369	[illegible] 1	24	41 7	0 36
7	5	107	137	83	107	[illegible]0	7	11	[illegible]	1 07	130	0 313	3 1	9	[illegible]5 9	0 4[illegible]
	0	107	1[illegible]9	77	99	[illegible]0	8	11	2	1 16	126	0 [illegible]73				
	5	96	139	86	109	29	16	21	3	0 85	128	0 3[illegible]1				
	10	97	143	86	111	26	15	19	3	0 88	1[illegible]8	0 315	[illegible] 9	30	[illegible]9 5	0 44
	20	97	135	81	104	15	8	11	[illegible]	0 97	133	0 309				
	30	97	149	88	115	17	10	12	[illegible]	1 10	1[illegible]6	0 307	3 1	3[illegible]	[illegible]8 9	0 5[illegible]
	60	99	145	84	111	14	7	9	3	1 33	129	0 328				
	1[illegible]0	104	13[illegible]	74	99	14	8	9	1	1 23	130	0 291				
	180	109	148	81	111	18	8	13	3	1 47	113	0 [illegible]79	3 7	34	[illegible]3 7	0 54

Table II (cont)

Pat no	Time (min after inj)	HR (min⁻¹)	Pressures (mmHg) Aorta S	D	M	Pulm artery S	D	M	CV	(dp/dt)m Aorta (mmHg× ms⁻¹)	PEP (ms)	PEP/LVET	CI (l× min⁻¹ m⁻²)	SI (ml× m⁻²)	PVRI (mmHg× min× m²×l⁻¹)	SWI (J×m⁻²)
8	5	54	161	79	108	20	10	13	2	0 77	72	0 171	2 1	42	34 8	0 68
	0	52	174	75	99	20	8	13	5	0 96	65	0 150				
	5	69	137	79	101	34	20	27	9	0 52	128	0 292				
	10	65	151	81	106	28	15	20	8	0 54	125	0 292	1 9	30	40 3	0 44
	20	61	164	83	112	27	14	20	8	0 63	119	0 280				
	30	59	165	80	111	26	10	17	6	0 61	117	0 282	2 3	40	36 0	0 65
	60	57	178	76	112	25	11	17	5	0 70	91	0 207				
	120	65	173	79	113	28	12	19	7	0 96	90	0 202				
	180	65	166	77	108	29	10	18	7	0 87	80	0 189	2 3	42	34 9	0 68
9	5	84	87	61	73	40	20	28	3	0 64	111	0 247	1 8	23	33 0	0 20
	0	73	92	66	76	40	12	22	1	0 68	115	0 260				
	5	101	73	59	65	42	28	33	5	0 32	157	0 359				
	10	100	70	58	62	43	28	34	7	0 29	164	0 364	1 3	13	33 8	0 06
	20	101	86	71	77	48	30	37	7	0 40	145	0 327				
	30	101	86	68	75	49	29	37	6	0 46	136	0 322	1 2	12	46 9	0 08
	60	99	95	75	84	55	29	41	8	0 47	115	0 258				
	120	101	98	70	83	62	33	45	6	0 81	94	0 225				
	180	94	90	67	77	56	30	41	5	0 53	102	0 234	1 1	11	54 1	0 08

central on were taken and the results of these determinations will be presented later

The patients were observed continuously and interviewed about side-effects at regular intervals Dryness of mouth and chest discomfort were the only side-effects specifically asked for

In no case did the injection have to be interrupted because of side-effects The catheterization procedure was complicated in all cases In patient 5 however both coronary and aortic catheterization failed and reliable dilution curves were not obtained The hemodynamic effects of DE are therefore based on the remaining eight patients

The statistical significance of differences between mean values was evaluated by applying the *t* test to intraindividual differences The following probability (*p*) levels of significance were used $p<0.001$ $p<0.01$ $p<0.05$ and $p>0.05$ The term significant as used in the text refers to the previously mentioned probabilities except $p>0.05$ For the variables for which data were derived both 5 min before and at the start of the injection the means of these two were taken as the initial value in the statistical calculations

RESULTS

Hemodynamic effects

Individual hemodynamic values are presented in Table II

Heart rate Individual control values varied from 52 to 119 beats/min Five minutes after DE HR increased in patients 3 6 8 and 9 A slight decrease was seen in the rest of the patients An average increase from 86 to 92 beats/min in all eight patients 5 min after injection was not significant (Fig 1)

Aortic pressures (Fig 1) The average mean aortic pressure (MAP) showed no change during the first 10 min following injection From the 20th min to the end of the observation period MAP was significantly increased above the control level Systolic aortic pressure (SAP) showed an insignificant average drop from 133 to 123 mmHg 5 min after the injection During the next 55 min SAP gradually increased and a level significantly above the control value was seen from the 60th min In three patients (nos 6 8 9) however SAP fell 20–30 mmHg within 5–10 min after the start of the injection Patient 9 with an initial SAP of 90 mmHg showed a minimum value of 70 mmHg after 10 min After that SAP increased rapidly and exceeded the initial value within one hour Diastolic aortic pressure (DAP) rose upon injection by an average of 5 mmHg and this change was significant ($p<0.05$) From 20 to 60 min after the injection DAP showed a statistically significant increase of about 6 mmHg

Pulmonary artery pressures (Fig 2) Initial diastolic PAP (DPAP) was 12 mmHg or less in five

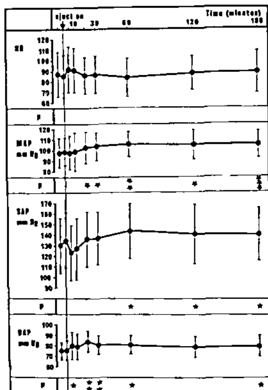


Fig 1 Changes in heart rate (*HR*) mean (*MAP*) systolic (*SAP*) and diastolic (*DAP*) aortic pressures following injection of disopyramide (mean values +S D)

patients and 20 mmHg or more in three Average DPAP increased from 14 mmHg before to 22 mmHg 10 min after the injection ($p<0.001$) From the 20th min an average increase of 3–4 mmHg above the control level persisted throughout the 3 hour observation period Patients 3 6 and 9 with high initial DPAP values (28 24 and 20 mmHg respectively) showed increases to about 30 mmHg and this pressure level in patient 9 persisted throughout the observation period In patient 4 no change in DPAP was seen following the injection

Central venous pressure Control values were normal in all patients Following DE CVP showed a significant but brief increase ($p<0.01$) (Fig 2) The highest value did not exceed 13 mmHg in any of the patients

Cardiac index (Fig 3) Ten minutes after DE all patients showed a fall in CI (average reduction 0 4 $l \times min^{-1} \times m^{-2}$ range 0 1–0 5 $l \times min^{-1} \times m^{-2}$) When measured 20 min later CI had returned to or was slightly above the control value in four patients in three (nos 1 3 7) CI had risen above the 10 min value but did not return to the control value until after 60 min In patient 9 CI showed no significant recovery with a 3 hour value of 1 1 $l \times min^{-1} \times m^{-2}$

Stroke index (Fig 3) The average control value was 30 $ml \times m^{-2}$ with individual values less than 25 $ml \times m^{-2}$ in patients 1 6 and 9 The 10-min value represented an average fall of 5 $ml \times m^{-2}$ ($p<0.05$) the most marked individual reactions being seen in patients 3 6 8 and 9 (10–12 $ml \times m^{-2}$)

Maximal first derivative of the aortic pressure curve decreased upon injection in all patients reaching a minimum value after 5 min which ranged from 41 to 76% of the control level Within the next 55 min there was a gradual increase to an average value 12% below the preinjection level (not significant) A slight but non significant reduction persisted for the last two hours of observation (Fig 4)

Systolic time intervals The group means for PEP

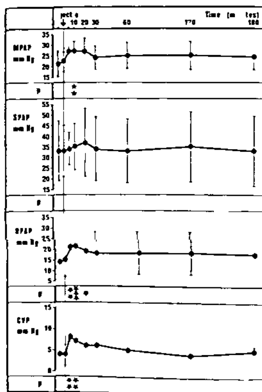


Fig 2 Effects of i v disopyramide on mean (*MPAP*) systolic (*SPAP*) and diastolic (*DPAP*) pulmonary artery pressures as well as effects on central venous pressure (*CVP*) (mean±S D)

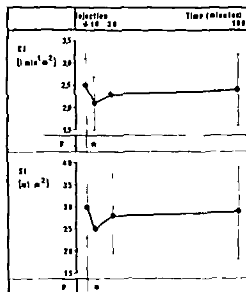


Fig 3 Cardiac index (*CI*) and stroke index (*SI*) changes following disopyramide (mean±S D)

and PEP/LVET showed largely parallel changes as shown in Fig 4 Both variables showed highly significant increments 5 and 10 min after the injection remaining significantly elevated for up to one hour Patient 7 showed no change in either PEP or PEP/LVET In patients 1 3 4 and 8 the maximum increases in PEP/LVET amounted to 50% or more

Peripheral vascular resistance index increased in patients and statistically significant increments ($p<0$ 05) were obtained both 10 and 30 min after the (14 and 15% respectively) (Fig 5)

Stroke work index A small but significant decrease of the mean ($p<0$ 05) was obtained 10 min after the injection (Fig 5) Patients 6 and 9 showed reductions as large as 50 and 70% respectively In one of them (no 9) with a low initial SWI (0 20 $J \times m^{-2}$) a marked reduction was still present three hours after the injection (0 09 $J \times m^{-2}$) Patients 1 2 4 and 7 showed no definite changes in SWI

Effect on arterial blood gases and acid–base balance

Compared to control values there were no significant effects on the arterial blood gases pH or base excess values 30 min after the injection

Electrocardiographic effects

PQ intervals showed a mean increase of 1 4 cs ($p<0$ 01) when measured 5 min after the injection The increase was most pronounced in patient 5 (4 5 cs) absent in patient 7 and had generally disappeared 30 min after the injection (Fig 6) Patient 3 developed tachycardia for about 10 min following the injection and a P wave following directly after an inverted T wave making it impossible to estimate the PQ and QT times accurately In patient 6 who also developed a tachycardia the P waves decreased in amplitude from the 4th to the 6th min and were indiscernible to the 12th min A nodal or ventricular rhythm probably prevailed during this period

QRS time (Fig 7) The 5 min value was 1 6 cs higher than the control value ($p<0$ 01) and a significant prolongation persisted 20 min after the injection The most marked increase in QRS time (5 cs) was seen in patient 3

QT time (Fig 8) Changes occurring 5 min after the injection could not be followed in patients 3 and 6 for the same reason that prevented an estimation of the PQ time The remaining patients showed a

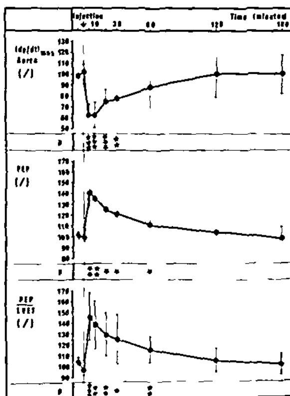


Fig 4 Maximal derivative of the aortic pressure curve ($(dp/dt)_{max}$) and systolic time intervals (*PEP* and *PEP/LVET*) in relation to time after injection of disopyramide (mean±S D)

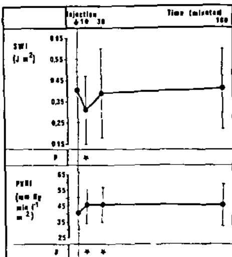


Fig 5 Effects on stroke work index (*SWI*) and peripheral vascular resistance index (*PVRI*) after injection of disopyramide (mean±S D)

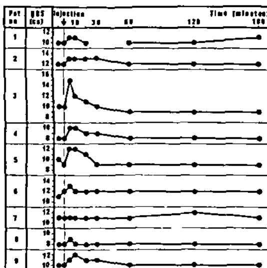


Fig 7 Individual values for QRS times before and after disopyramide

mean increment of 4 cs ($p<0.01$) In four cases (nos 4 5 8 9) the increases after 10 min amounted to 5–9 cs A widening of the T wave contributed to a prolongation of the QT time Compared to the changes in PQ intervals and QRS times the increases in QT times lasted longer and were still discernible one hour after the injection in three patients

Ventricular ectopic beats (Fig 9) Wide variations in the control frequency of VEBs were recorded 10–60 min before the injection In patients 4 6 and 7 the number was below 10/min in patients 3 and 8 it was between 10 and 20 patient 9 varied between 1 and 14 VEBs/min usually with two or

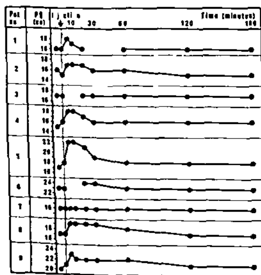


Fig 6 Individual values for PQ times before and after disopyramide

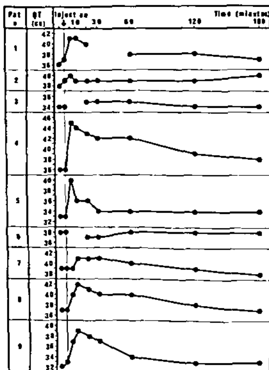
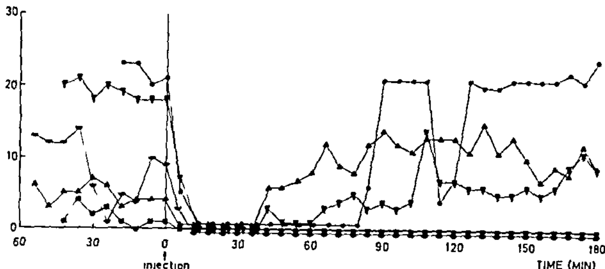


Fig 8 Individual values for QT times before and after injection of disopyramide



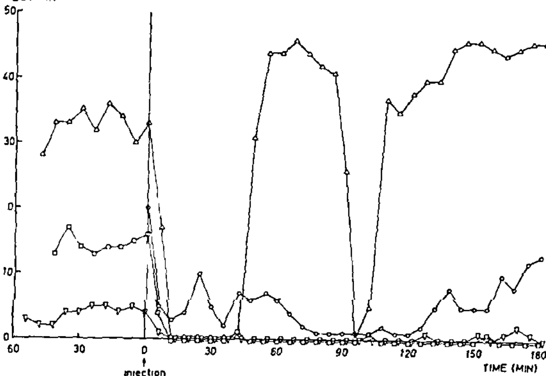


Fig 9 Individual variations in the frequency of ventricular ectopic beats (*VEBs*) for up to 60 min before and 180 min after the injection of disopyramide Symbols as in Table I

three in sequence patients 1 2 and 5 had a VEB frequency above 20/min Following DE injection the number of VEBs fell rapidly All patients but one (no 1) became completely free from VEBs within 3 min after the start of the injection In patient 6 arrhythmia was abolished during the first minute in patients 2 3 and 8 during the 2nd and in patients 5 7 and 9 during the 3rd min After about 40 min VEBs returned in patients 6 and 8 and there was a gradual increase in the VEB frequency In patient 5 the VEB frequency rose steeply after about 40 min and even exceeded the control level In patient 2 VEBs returned after about 80 min Four patients (nos 3 4 7 9) were almost or completely

free from VEBs during the entire 3 hour observation period Patient 1 displayed a marked decrease in the number of VEBs after the DE injection but during the second half of the study the frequency gradually increased

Subjective side effects

All patients except no 9 experienced side effects These were tolerable in all patients but one (no 5) Dryness of the mouth (usually 10–60 min after the injection) occurred in six patients (nos 2 3 5 6 7 8) A feeling of warmth 1–3 min after the injection was experienced by patients 1 4 and 8 Urinary urgency was felt immediately after the injection by patient 5 who also noticed difficulties in micturating for about one hour after the injection Patient 8 complained of a brief blurring of vision Two patients (nos 5 and 6) experienced dyspnoea between the 4th and 15th min after injection In patient 6 this was not accompanied by any visible signs of laboured respiration whereas patient 5 looked pale and dyspnoic for a few minutes This patient however had had several similar attacks spontaneously during her hospital stay and during the study there were no extreme changes in any of the directly recorded variables or in the ECG complexes Patients 1 and 5 experienced brief dizziness and patient 3 some tiredness during the first 30 min

DISCUSSION

The drugs currently available for the treatment of ventricular tachyarrhythmia are generally felt to be insufficient and limited by inefficacy and toxicity (16 19) The usefulness of i v disopyramide in the treatment of ventricular arrhythmias has been documented in animals (13) and suggested in man (1) The effectiveness of i v DE in suppressing VEBs is strongly indicated by the present findings Thus the drug caused complete cessation of VEBs in eight of the nine patients and the ninth showed a markedly reduced number of VEBs

A negative inotropic effect of DE has been demonstrated in animal experiments (11 13) Such an effect was also clear from the present data viz significant reductions of CI SI and SWI as well as an increase of DPAP The present reduction of the group mean for CI by 16% agrees well with the 14% reduction in Q reported earlier in man following 2 mg of i v DE (1) As other studies (10 14) have demonstrated that systolic time intervals and $(dp/dt)_{max}$ of the central aortic pressure curve are reliable indices of cardiac muscle contractility the observed changes in these variables further reflect the reduced cardiac contractility due to DE The duration and magnitude of the reductions in SI and CI after the administration of DE in the dose given were more marked than the corresponding changes reported for lidocaine in therapeutic doses (3 17) The same holds true when the present results are compared with reports on the effect of diphenyl hydantoin (9) and procainamide following acute myocardial infarction (12)

As demonstrated for other antiarrhythmic drugs e g for lidocaine (3) however the negative inotropic effect of DE is in all likelihood related to the dose The complete or almost complete abolition of VEBs in four of nine patients for at least three hours after i v administration of DE suggests that the optimal therapeutic dose may have been lower than that used in the present study Therefore it cannot be ruled out that the negative inotropic effect for comparable doses with respect to antiarrhythmic effects is similar or possibly smaller for DE than for the above mentioned drugs

The present study was concerned with the effect of i v DE in patients with ventricular extrasystoles in the presence of various degrees of cardiac decompensation and/or signs of stable coronary artery disease It is of interest to note therefore that in the eight patients in whom the measurements of Q and arterial BP could be made the negative hemodynamic effect as reflected in these variables was not associated with clinically apparent deleterious effects and that adverse side effects were tolerable Most of the observed side effects could be attributed to the anticholinergic properties of DE which have been reported earlier (19) In patient 5 however with severe heart failure due to congestive cardiomyopathy it seemed clear that DE in the dose given precipitated an attack of dyspnoea but this symptom was brief and for about 40 min it was the relief from symptoms of persistent premature beats which predominated

One would expect that the patients with the most obvious signs of depressed cardiac function prior to drug administration would show the greatest susceptibility to the negative inotropic effects of DE Inspection of individual responses suggested that this was the case Three of the patients with high control values for DPAP (nos 3 6 9) also showed changes following DE which were among

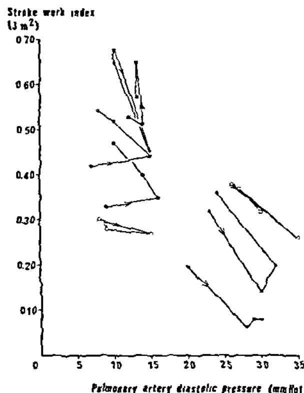


Fig 10 Stroke work index in relation to pulmonary artery diastolic pressure in 8 patients following injection of di sopyramide Loop direction is indicated by arrow Symbols as in Table I

. largest observed for CI SI $(dp/dt)_{max}$ of the .l aortic pressure and SWI Furthermore the DPAP in these patients rose to high values although without signs of dyspnoea except in case 6 Among the measured variables however the DPAP seemed to be the only one which could be used for a quantitative prediction of DE s negative inotropic effect This relationship could be well demonstrated by using a modified Frank–Starling diagram with DPAP on the abscissa and SWI on the ordinate (Fig 10)

In cases with signs of cardiac failure prior to the present study conventional treatment was thought to be optimal It is conceivable that the ventricular arrhythmia contributed to the cardiac decom pensation still present in several of the patients when DE was administered Following DE the absence of further significant clinical deterioration despite a reduction in cardiac contractility can reasonably be attributed to the suppression of the ventricular arrhythmia The group mean for MAP showed no reduction indicating that the normaliza tion of the cardiac rhythm due to DE was accompanied by arterial vasoconstriction possibly via baroreceptor reflexes thus compensating for the reduced cardiac output

The ECG findings following DE with a pro longation of the PR QRS and QT times agree with observations in animals showing a fairly linear in crease in QRS and PQ times with dose (11 13) However studies in man with His bundle record ings and i v doses of 1–2 mg/kg b wt (7) did not generally show changes in conduction time through the A–V node or His Purkinje system In the pres ent study individual changes in the ECG were dose related (unpublished data) but there was no clear correlation between changes in contractility and the ECG in individual patients In view of the observed ECG changes it is obvious that A–V block II–III and/or marked conduction disturbance should be considered as contraindications to the use of DE but in the present study the changes in the time intervals of the ECG were not exaggerated in the patients with prolonged control values for these variables Increased automaticity probably in Pur kinje fibers with high doses of DE could be the explanation for the tachycardia seen in patient 6

It can be concluded that the DE dose in the pres ent study was effective in suppressing ventricular arrhythmia Like other antiarrhythmic drugs DE possesses a depressive effect on cardiac function and there were signs that this effect may be of clinical importance in patients with high filling pres sures of the left ventricle As patients requiring antidysrhythmic drug therapy commonly show signs of cardiac decompensation and earlier reports on DE in man have not demonstrated significant negative hemodynamic effects it was decided in the present study not to exclude patients with hemo dynamic evidence of deteriorated cardiac function The maintenance and elevation of the mean systemic arterial pressure following DE in spite of deranged myocardial function suggests that vaso constrictor reflexes are preserved with this drug Presumably DE possesses only limited vasodilator effects and less so than procainamide and quin idine (5 13) Such properties justify the use of DE in slow injection

Further studies comparing hemodynamic and antiarrhythmic effects of DE with other antidys rhythmic drugs are needed It seems likely how ever that smaller doses than those used in the pres ent study or a slower administration rate should be used in future investigations

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Evaluation of a Computer-based System for Detecting Ventricular Arrhythmias

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ABSTRACT A digital system for real time arrhythmia monitoring in the coronary care unit has been designed. The system is based on an algorithm for discrimination between normal complexes and ventricular ectopic beats (VBs). A beat is classified as normal if the absolute difference from a running average of the patient's normal QRS is below an adaptive threshold. To prevent artifacts and beats of non ventricular origin from being falsely interpreted as VBs, each abnormal beat is correlated with a typical VB waveform incorporated into the program. A VB is recognized only when the correlation coefficient exceeds 0.8. In a performance study, ECGs from 15 patients were recorded on magnetic tape and replayed to the computer. Independent evaluation by two physicians showed a total of 1306 VBs, 94% correctly classified by the computer. In the group labelled "suspected VBs" the detection rate was lower (average 69%). Out of the whole number of complexes (53260) 0.45% were falsely interpreted as VBs by the computer. Artifacts giving rise to false VBs are included in this figure. The causes of false positive and false negative VBs were thoroughly investigated and on the basis of these results, possible improvements in the system are discussed.

With the introduction of ECG monitoring of patients with acute myocardial infarction, mortality in this disease has dropped from about 35 to 20%, mainly due to improved treatment of cardiac arrhythmias (5). Conventional ECG monitoring is based on automatic systems for heart rate (HR) alarms, preferably combined with a nurse observing an oscilloscope or a continuous ECG paper recording with slow speed. Despite the relatively good results achieved with this type of monitoring, it is quite clear that a lot of information is lost. The HR-dependent alarm does not differentiate normal complexes from ventricular ectopic beats (VBs) and the human observer is often disturbed by other activities. The monotony of watching a multichannel oscilloscope may also result in periods of reduced attention. One retrospective study comparing results from conventional ECG monitoring with a continuous recording has shown that less than 20% of the serious arrhythmias thought to precede ventricular fibrillation were detected (8). In another study with nurses watching oscilloscopes, 70% of all episodes of ventricular tachycardia were overlooked (6).

To overcome the problems associated with conventional ECG monitoring, computer technics have been utilized (2, 3, 4, 7). So far, however, no ideal system exists and only a few have been thoroughly evaluated.

TECHNICAL DESCRIPTION

The monitoring system described in this paper utilizes a Datasaab D5/30 minicomputer located in the CCU. The computer has a core memory of 16 K 16-bit words but no bulk memory. It is equipped with an A/D converter for ECG input from eight beds. ECG on/off and alarm reset controls, connected to digital input channels, have been added to the existing bedside units. Communication with the computer is provided via an α numeric video terminal. The arrhythmia monitoring software provides a beat-by-beat real time analysis of the ECG. The program organization is illustrated in Fig. 1.

Sampling and R wave recognition. Th

This paper was presented in part at the first World Conference on Medical Informatics, Stockholm, Sweden 1974.

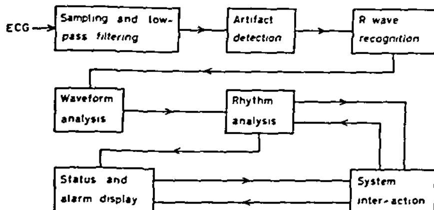


Fig 1 Block diagram of program organization

gram has the highest priority and is scheduled every 10th ms After digital low pass filtering (30 Hz cutoff) the first difference of the ECG is computed and stored in a circular buffer of 512 8-bit words for each patient A direct artifact detection is also performed permitting automatic rejection of low-quality ECG portions Whenever the derivative of the ECG or a baseline shift exceeds certain limits the waveform analysis is blocked for 2 sec R wave recognition is performed using an adaptive threshold (*d*) for the ECG derivative (Fig 2) An R wave is recognized whenever the following three sequential criteria are fulfilled within an interval of 0 25 s (*A*) positive derivative exceeding threshold (*d*) (*B*) negative derivative exceeding *threshold (d/2) (C) signal returning to baseline or derivative* below threshold (*d/2*) This logic procedure prevents most P and T waves from entering the waveform analysis When an R wave is recognized the previous R-R interval and the position in the buffer is passed to the waveform analysis program

Waveform and rhythm analysis For each R wave 200 ms of sampled data are compared with the running average of the patient s normal QRS complex This reference complex is computed initially from the first 10 sec of the ECG after pressing the bedside ECG control button A new complex is considered normal if the sum of absolute differences between corresponding sample points (δ) satisfies the unequality $\delta \leq \bar{\delta}$ c where $\bar{\delta}$ is a running average of the sum of absolute differences for complexes judged as normal and c is a constant set to 3 0 A beat regarded as normal is also added to the running average complex with a time constant corresponding to 32 beats Hence slow spontaneous waveform changes will not prevent the recognition of normal QRS complexes

With the aim of separating VBs from artifacts and beats of supraventricular origin each abnormal complex is correlated with a typical VB waveform a technique also used by Feezor et al (1) in an analog preprocessor The waveform used in this program was computed as an average VB from earlier ECG recordings from a number of *patients and incorporated into the program as 320 ms of* sampled data (Fig 3) An abnormal complex is marked as ventricular if the absolute value of the normalized cross correlation coefficient between the complex and the stored VB waveform exceeds 0 8 If the basic rhythm is regular a waveform approved as ventricular is classified as a VB only *if* it is preceded by an R-R interval shorter than 90 % of the running average and followed by a compensatory pause The basic rhythm is considered regular *if* the running standard deviation of R-R intervals is less than 8 % of the average R-R interval

MATERIAL AND METHODS

To evaluate the performance of the VB detecting algorithm a single lead ECG from 15 patients with various types of ventricular arrhythmias was recorded on magnet

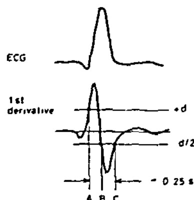


Fig 2 Schematic drawing illustrating the principle for R wave recognition For explanation of symbols see text

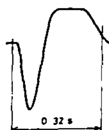


Fig 3 Stored waveform for typical ventricular ectopic beat

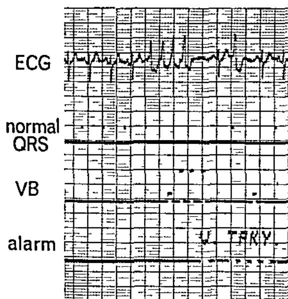


Fig. 4. Sample recording from the computer analysis.

ic tape via the central monitoring station and replayed later to the computer. The electrodes were placed over the sternum. Taped ECGs were also transferred to paper charts (speed 10 mm/sec) for independent evaluation by two physicians. Each abnormal complex or potential was numbered and classified by both interpreters and the results were compared later with the computer interpretation.

Subjective, generally accepted criteria for classification were used by the physicians and each complex was placed in one of the following five classes: *V* = ventricular ectopic beat, *A* = abnormal complex of possibly ventricular origin, *N* = abnormal beat, probably of non ventricular origin, *O* = ordinary beat, *X* = artifact. The *V* class included ventricular escaped beats and fusion beats. The *V* and *A* groups also contained complexes disturbed by artifacts. Supraventricular ectopic beats with normal conduction were assigned to the *O* category. Complexes classified as VBs by the computer and not discovered by the physicians were reexamined, but in all cases classified as essentially normal or artifacts. Only one opportunity for classification was given to the interpreters, who lacked detailed knowledge of the computer algorithms. No changes in the computer algorithms or criteria for classification were undertaken during the study and no recording was omitted because of difficulties in interpretation.

The results of the computer interpretation were presented on a 4-channel mingograph with a paper speed of 10 mm/sec (Fig. 4). For comparison between interpretation by the computer and the physicians a special diagram was used (Fig. 5). This diagram defines the final diagnosis of a complex and the computer classification was compared with this diagnosis.

After classification of the ECG, the paper recordings were reexamined by one physician and abnormal complexes with similar QRST shape were put together in groups. The number of such groups in each patient was counted. QRS width was estimated as the average value from five normal complexes in a 50 mm/sec ECG recording.

RESULTS

Characteristics of the ECG material are given in Table I. The duration of the records varied between 5 and 85 min (mean 37). A total of 53 260 complexes were analysed. Out of these, 2781 (5.2%) were considered abnormal by the physicians. Nine patients had sinus rhythm, and six had atrial fibrillation. Bundle branch block or conduction disturbance was present in a majority of the patients—eight recordings showed a QRS time of 0.10 sec or more. The number of abnormal waveform groups in each patient was usually high, with a mean of 5, range 1–10.

Table II gives the individual and total results for the comparison between ECG classification by the physicians and the computer. In the VB group, totally 1306 complexes, 94% were correctly classified as VBs by the computer. Individual percentages varied between 74 and 100. In patients 5 and 13 the number of definite VBs was very low. In

Dr A \ Dr B classification	V	A	N	O	X
V	I	II		III	
A		II			
N			IV		
O		III		V	VI
X				VI	VI

Fig. 5. Diagram used for comparison between interpretation by the computer and the physicians. After classification by the physicians (for explanation of classification symbols, see text) an abnormal complex or event was located in one of the six areas: *I* = VB, *II* = suspected VB, *III* = divergent interpretation between physicians, *IV* = abnormal supraventricular complex, *V* = ordinary complex (false VB), *VI* = artifact (false VB). Computer VBs were marked in the upper left triangle of each square and computer non VBs in the lower right triangle.

T ible I *Characteristics of the ECG material*

Pat no	Time (min)	Total no of beats	No of abnormal beats	Abnormal/Total (%)	Sinus rhythm	QRS time of normal complexes (sec)	No of abnormal wave form groups
1	54	5 690	121	2 1	Yes	0 06	1
2	25	2 400	51	2 1	Yes	0 05	3
3	14	1 400	205	14 6	No	0 11	7
4	10	830	283	34 1	Yes	0 10	2
5	85	7 820	33	0 4	Yes	0 07	2
6	50	4 680	232	5 0	No	0 11	5
7	28	3 520	286	8 1	No	0 08	9
8	9	740	35	4 7	Yes	0 10	4
9	22	2 450	291	11 9	No	0 09	10
10	5	350	217	62 0	Yes	0 10	2
11	55	4 450	213	4 8	Yes	0 11	4
12	80	6 210	159	2 6	Yes	0 07	4
13	21	1 270	300	23 6	Yes	0 12	3
14	55	4 980	168	3 4	No	0 14	6
15	45	6 470	187	2 9	No	0 09	6
Total	558	53 260	2 781				
Mean	37	3 550		12 2			5

the suspected VB category VB markings resulted in 511 of 743 complexes or 69%

If patients with less than ten complexes were omitted the individual results varied between 11% (no 7) and 99% (no 13) If the VB and suspected VB group are combined correct classification by the computer was achieved in 85% Divergent interpretation was seen on 221 occasions with 24% computer VB markings In three patients (nos 7 9 11) the number of complexes in this category was relatively high varying between 32 and 92 A total of 511 abnormal beats were diagnosed as probably

ble II *Comparison between ECG classification by the physicians (P) and by the computer (C)*

Pat no	P: VB		Suspected VB		Divergent interpretation		Abnormal complex non VB		Normal	Artifact
C	VB	Non VB	VB	Non VB	VB	Non VB	VB	Non VB	VB	VB
1	117	3	0	1	0	0	0	0	0	3
2	31	0	12	4	1	1	0	2	0	0
3	37	0	27	87	2	7	18	27	3	3
4	277	3	0	0	1	0	0	2	0	0
5	2	0	10	19	1	0	0	1	0	2
6	186	37	3	4	1	0	0	1	1	0
7	174	20	2	17	4	28	2	39	3	0
8	29	1	3	1	1	0	0	0	0	0
9	66	12	41	9	17	36	63	47	4	0
10	99	1	0	0	0	0	0	117	0	4
11	20	7	24	26	4	88	10	34	1	14
12	150	0	0	0	7	2	0	0	0	7
13	1	0	279	2	8	3	4	3	0	3
14	23	0	5	3	2	0	29	106	0	0
15	10	0	105	59	3	4	0	6	60	4
Total	1 222	84	511	232	52	169	126	385	72	40
% within each group	94		69		24		25			
Range (%)	74–100		0–99		4–100		0–57			
% of total no of complexes							0 24		0 14	0 08

Table III *Missed VB detection (groups I and II in Fig 5)*

Cause	Patient number 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
QRS detection inhibited by artifacts	3								1						
Prematurity/compensatory pause absent	1	1		3			4	1	14	1	9		1	3	1
QRS narrow/low correlation with prototype VB		3	86		19	4	29		6		24				58
Missed QRS detection (low derivative)			1			4	4								
Classified as normal						33		1					1		

non ventricular 25% of these fell out as VBs in the computer analysis In patient 9 more than 50% of the probably non ventricular beats were diagnosed as VBs by the computer Seventy two normal beats were marked as VBs 60 of these could be referred to patient 15 There were 40 false VB markings due to various forms of disturbances in the ECG signal The sum of false VB markings corresponded to 0 45% of the total number of complexes

The main reasons for missed VB detection among definite and suspected VBs are shown in Table III Inhibition of QRS detection due to artifacts occurred rather infrequently Lack of prematurity and/or absence of compensatory pause was the second most important reason for missed VB detection occurring in a majority of the patients and totally 39 times On 229 occasions VBs were rejected by the computer due to a narrow initial part of the QRS complex and/or a low correlation with the prototype VB In patients 3 and 15 a total of 144 VBs were not diagnosed for this reason In a few cases a low derivative of the VB prevented proper identification of the R wave Thirty five VBs with only minor deviations in appearance from the normal complex were falsely interpreted as normals

Table IV *False VB detection (groups IV V VI in Fig 5)*

Cause	Patient number 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Minor artifact on normal or essentially normal QRS	1		2								5	4			2
Baseline artifacts	2		1		2						9	2	3		
Narrow and high/low amplitude ectopic beat			18				2		63		10		4	29	
Essentially normal high or low amplitude complex			3				3		2		1				60
Repolarization phase of VB interpreted as a VB										4		1			2
Unknown						1			2						

Table V *Comparison between classification in patients with sinus rhythm and atrial fibrillation (percentage computer VBs within parentheses)*

P=physicians C=computer

P	VB		Suspected VB		Divergent interpretation		Abnormal complex non VB		Normal	Artifact
C	VB	Non VB	VB	Non VB	VB	Non VB	VB	Non VB	VB	VB
Sinus rhythm	726 (98)	15	328 (86)	53	23 (20)	94	14 (8)	159	1	33
Atrial fibrillation	496 (88)	69	183 (51)	179	29 (28)	75	112 (33)	226	71	7

Table IV presents the causes of false VB detection In 33 cases various forms of artifacts were interpreted as VBs by the computer Ectopic beats of non ventricular origin resulted in misdiagnosis on 126 occasions and formed the largest group of false positive VBs Half of these complexes were recorded in patient 9 Variations in the amplitude of the normal QRS complex resulted in 69 false positive VBs 60 of these were seen in patient 15 In 3 patients a few VB markings could be ascribed to the repolarization phase of the preceding VB

In the patients with sinus rhythm there was a higher figure for correct classification among definite and suspected VBs (Table V) The difference was insignificant among the complexes which resulted in divergent interpretation by the physicians False VB classification was much more common among patients with irregular rhythm

DISCUSSION

Proper classification of ectopic beats from a single lead ECG may be difficult if not impossible even for a trained human observer particularly in patients with conduction defects and irregular rhythm In this group VBs may be narrower than the normal complexes and P waves and prematurity criteria may not be used for the diagnosis

In the present study the recorded time varied derably between the patients To some extent was because we had decided to stop the num- of abnormal complexes after about 300 correct computer classification of definite and suspected VBs in patients with a recording time above average was 76% and in patients with a recording time less than 37 min 86% The average of the individual percentages for correct classification is 81% which is only slightly less than the overall figure (85%) indicating that the total number of complexes in patients with high correct computer classification was slightly larger than the number from patients with a lower detection rate

Three of our patients (nos 6 7 8) also belonged to the material used in the development of the recognition program The average VB detection rate in these patients was 83% A comparison with the overall figure for the whole material (85%) indicates that no bias was introduced

Average QRS width was 0 08 sec in the patients with sinus rhythm and 0 11 sec in those with atrial fibrillation Also the number of waveform groups was higher in the patients with atrial fibrillation These differences as well as the decreasing significance of prematurity for distinguishing between normal and abnormal complexes help to explain the differences in the results of the computer classification between patients with regular and irregular rhythm (Table V) The proportion of complexes in the groups labelled VB and suspected VB is about the same in patients with sinus rhythm and atrial fibrillation

With the present algorithm a beat with a width of the first deflection of the QRS complex less than 0 07 sec will not be classified as a VB This criterion as well as a low correlation with the prototype VB resulted in a high figure for false negative usually biphasic and rSR-configurated VBs These complexes occurred more frequently among patients with atrial fibrillation and were the major reason for the high proportion of missed VBs in patients with irregular rhythm Artifacts were responsible for about 16% of all false VBs but surprisingly patients with atrial fibrillation contributed very little to this figure In the group essentially normal high or low amplitude complexes (Table IV) the majority of complexes resulted from sudden changes in the QRS amplitude of the normal complexes Atrial fibrillation probably contributed to the high number of false VBs for this reason in patient 15

For a majority of the patients in this study the accuracy of VB detection is satisfactory from a clinical point of view Some patients however showed quite unacceptable figures for false positive VBs and the number of missed VBs in a few patients was rather high As in any system of this kind the design and the parameter settings of the diagnostic program are a compromise between the demands for sensitivity and specificity in VB detection A higher threshold for the correlation between abnormal QRS complexes and the prototype VB would certainly reduce the number of false VBs but would also increase the number of missed VBs Therefore we feel that in order to improve the system the present use of a fixed VB waveform should be replaced by a more flexible method for waveform recognition (10)

Although a number of computer based arrhythmia monitoring systems have been developed during the last five years only a few detailed evaluations have been reported Oliver et al (7) using a special system for data compression—the so-called

Aztec algorithm—grouped together complexes with similar shape A complex which could not be assigned to a normal group was classified as ventricular if it passed certain shape width and prematurity tests Signal amplification was adjusted at the start of the recording and this was the only adjustment allowed during the study Beat by beat classification revealed 4010 VBs 78% correctly classified by the computer Out of the whole material (50000 beats) 180 or 0 36% were falsely classified as ventricular a figure only slightly lower than ours Three of 34 patients had atrial fibrillation and another two had also periods of atrial fibrillation but no data are available to tell if there were any differences in performance between patients with regular and those with irregular rhythm

In a recent paper by Yanowitz et al (11) the accuracy of premature ventricular beat recognition by an on line computer system was evaluated in a prospective study Apart from a somewhat simplified diagnostic scheme the basic algorithms were essentially the same as those used by Oliver et al (7) However to allow optimum performance adjustments in certain parameters of the Aztec and recognition program were done prior to data analysis ruling out a fair comparison with the results of Oliver et al and ourselves Out of 33500 beats 25 false VBs were indicated by the computer (0 07%) and approximately 90% were correctly classified In this study three of 28 patients had atrial fibrillation with an average VB identification rate of 74% The search for ectopic beats was inhibited at a relatively low noise level which may partly explain the lower figure for false VBs in this material

A third system based on the Aztec algorithm is reported by Harrison et al (4) In a validation study computer diagnosis of VBs was compared with that of two cardiologists On an average 84% of all ventricular premature beats were correctly identified with a false positive rate of 0 14%

Another algorithm for real time arrhythmia monitoring has been described by Feldman et al (3) The recognition of an ectopic beat is based on a cross correlation technique comparing each beat with a normal complex stored for each patient at the beginning of the run A preliminary test of the accuracy of VB detection was performed on an ECG material comprising approximately 48000 beats Using a 10% prematurity criterion the overall VB identification rate was 80% Only 22 false VBs corresponding to 0 05% of the total number of complexes were reported However no data are given on the basic rhythm of individual patients

Since different investigators have used their own set of test tapes and also their own validation procedures a comparison between different systems is very difficult It can be noted however that the VB detection rate for four of the systems discussed lies within the range of 78–85% A somewhat higher precision was obtained in the fifth system evaluated by Yanowitz et al (11) where parameters of the recognition program were adjusted for individual patients For reported figures of false positive VB detection there was a greater variation between the systems (0 05–0 45%) To some extent this divergence may reflect differences between the noise levels of the different ECG materials Thus Yanowitz et al state that there was no real noise problem during data collection while in our study several patiens exhibited major artifacts that in the present parameter settings did not inhibit QRS or VB recognition However in our material the main cause of false VBs was not artifacts but abnormal beats of non ventricular origin being falsely classified as ventricular Whereas Oliver et al (7) report 0 27% supraventricular complexes with aberrant conduction our figure was 0 96% In the other three investigations there are no data on the proportion of abnormal non ventricular beats

Vetter and Julian (9) evaluating the alarm functions of a special purpose hybrid computer found that 99% of all alarm situations were detected However no data from a beat by beat analysis were reported and the results cannot be directly compared with the other systems discussed above

We hope that in the near future the Evaluation Group for Arrhythmia Detectors (2) will provide test tapes containing an adequate number of arrhythmias and various ECG wave forms to permit a proper comparison between systems A monitoring system optimized to such a material however will be difficult to compare with other systems To avoid problems of this kind the principles of evaluation should preferably be the same for all groups utilizing the test material

Finally it should be emphasized that accurate VB detection is only one—although important—prerequisite for the acceptance of a computer based system for ECG monitoring To complete the evaluation long term studies of the system in clinical routine work will be needed

ACKNOWLEDGEMENTS

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Beta$_1$-blocker (Practolol) and Exercise in Patients with Chronic Obstructive Lung Disease

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ABSTRACT Ventilatory and circulatory data from 20 patients suffering from chronic obstructive lung disease have been obtained before, during and after exercise at 600 kpm/min for 5 min on a bicycle ergometer The patients had been given intravenously practolol, 15 mg, or saline alternatively, using a double blind cross-over technique A slight postexercise reduction of FEV_1 (8%) was noted after practolol medication as compared to placebo with an accompanying decrease in P_aCO P_aO_2 did not differ substantially No wheezing or inappropriate dyspnea attributable to the medication was noted in any of the patients The well known β_1 blocking effects on the circulation were confirmed, with maintained Q and reduced HR, together with a lowered systemic BP during and after exercise There was a significant positive relationship between the postexercise reduction of FEV_1 and the concomitant fall in HR It is concluded that practolol in doses with near maximal circulatory effects had a slight but clinically insignificant effect on the ventilatory parameters

Practolol is a cardioselective adrenergic β blocker with only slight effects on the bronchial adrenergic receptors (3) The antiarrhythmic and hypotensive effects of the drug have made it useful in cardiovascular disease but the clinical effect on the bronchial system in patients with chronic obstructive lung disease (COLD) is still under debate

The drug has been reported to precipitate bronchoconstriction in susceptible individuals (2 14 16) On the other hand several studies have not revealed a clinically significant deterioration in either ventilatory parameters or blood gases after practolol medication (4 7 11 13) Exercise studies in patients with COLD under the influence of practolol have been few and not systematic No clinically significant bronchoconstriction during or after exercise was observed in some asthmatic patients who were included in a group with angina pectoris (1 6) but a postexercise reduction of FEV_1 has been noted recently in normal subjects after practolol medication (12) There is therefore a lack of information on the clinical effects of practolol in patients with COLD

The present study was designed to clarify the ventilatory reaction in a group of patients with COLD under the influence of practolol particularly in connection with exercise corresponding to daily activity and to observe the relationship between the ventilatory and circulatory effects

PATIENTS AND METHODS

Twenty patients 3 women and 17 men mean age 53 0 years (range 33–71) suffering from COLD in a stable phase were included in the study Five had clinical and physiological signs of additional emphysema None of the patients were of the typical asthmatic type nor showed evidence of exogenic allergy Fourteen patients were on stable oral steroid treatment during the study None were given β_2-stimulators (i e salbutamol or terbutalin) or other sympaticomimetics during the period The study was made double blind cross-over comparing practolol (Eraldin® supplied by ICI Pharma Norway) 15 mg i v with placebo (saline i v) at 2 days interval

The study started at 9 a m The patient sat quietly and relatively comfortably on a mechanically braked bicycle ergometer (Monark Stockholm) for 5–10 min after which the baseline ventilatory and circulatory measurements were made Then the medication was given over a period of 1 min The ventilatory and circulatory measurements were repeated 5 min after the end of the injection (+5 min) The patient then exercised at 600 kpm/min for 5 min ventilatory and circulatory measurements being made the last minute (+10 min) The patient rested on the bicycle for 10 min (+20 min) and for a further 25 min (+45 min) ventilatory and circulatory measurements being obtained at both times

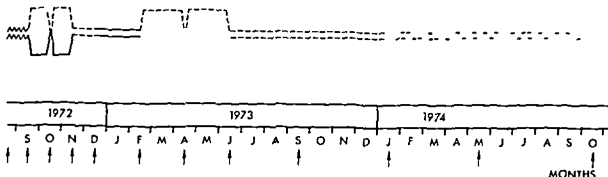


Fig 1 Designs of the clinical trials presented in this paper Arrows denote clinical examinations ~~~=alprenolol —=placebo – – –=metoprolol t i d =metoprolol b i d =propranolol

first week of each period half of this dose was given The patients returned for clinical examination at the end of each period (Fig 1)

After completing this cross-over study nine women had their metoprolol dose doubled (80 mg tartrate t i d) while 15 continued to take 40 mg t i d for a further four weeks During this second part of the study metoprolol was given according to a single blind pattern During these first phases of the trials with metoprolol all 24 women completed the study

The women were then admitted to a run in period on placebo for eight weeks followed by a double blind cross-over study comparing metoprolol with propranolol for eight weeks on each substance This study is presented separately (5) The women were then followed up for nother 16 months on metoprolol During the first 7 nths of this period metoprolol was given in a dose of 50 t i d and 100 mg t i d respectively Thereafter the ily dosage of metoprolol was reduced from 50 or 100 mg t i d to 50 or 100 mg b i d and the participants were again examined about 4 and 9 months after starting the b i d dosage regimen Twenty three women completed the follow-up phase of the study One woman was excluded due to a disease unrelated to her hypertension or its treatment

BP was measured by the same examiner and for each patient at the same time of the day Readings were taken from the right arm using a 30×12 cm cuff with nylon hooklet binding with a mercury sphygmomanometer The BP was read to the nearest 2 mm HR was registered in the seated position

Laboratory analyses were performed according to the routine methods of the Central Laboratory of Sahlgrenska sjukhuset Goteborg Serum uric acid was determined by an enzymatic method

Statistical methods Conventional statistical methods were used for calculation of mean and standard errors of the mean (S E) The significance of difference between sample means was estimated with Student s *t* test for the means of differences between paired observations In this way each subject acted as her own control throughout the study The differences were considered statistically significant for $p<0\ 05$

RESULTS

Comparison between metoprolol and placebo

Means of BP HR body weight and serum uric acid values at the end of the placebo and metoprolol periods during the cross-over study are shown in Table II Significant differences were found for BP in all positions measured and for HR while no significant difference was found for body weight Serum uric acid was significantly higher during treatment with metoprolol than on placebo but the difference was moderate and there were no high individual values (none ≥6 mg/100 ml) BP in the seated position at the last clinical visit on alprenolol before switching over to metoprolol and at the end of the placebo and metoprolol periods respectively is presented for each group

Table I *Pretreatment values of blood pressure heart rate body weight and serum uric acid in 24 women participating in the present investigation*

	Mean	S E
Systolic BP (mmHg)		
Seated	183	2 9
Supine	186	3 5
Standing	182	3 5
Diastolic BP phase 4 (mmHg)		
Seated	107	1 6
Supine	106	1 8
Standing	114	1 8
HR seated (beats/min)	87	2 7
B wt (kg)	71 2	3 7
Serum uric acid (mg/100 ml)	4 1	0 3

Table II *Blood pressure heart rate body weight and serum uric acid after four weeks on placebo and metoprolol respectively (n=24)*

	Placebo		Metoprolol		Significance of difference
	Mean	S E	Mean	S E	
Systolic BP (mmHg)					
Seated	148	2 6	140	3 3	$p<0\ 05$
Supine	152	3 0	143	3 3	$p<0\ 05$
Standing	153	3 1	146	3 5	$p<0\ 05$
Diastolic BP phase 4 (mmHg)					
Seated	91	1 3	87	1 5	$p<0\ 05$
Supine	92	1 7	88	1 5	$p<0\ 01$
Standing	100	1 1	93	1 2	$p<0\ 001$
HR seated (beats/min)	80	2 0	65	1 5	$p<0\ 001$
B wt (kg)	73 4	3 7	73 8	3 7	N S
Serum uric acid (mg/100 ml)	3 5	0 15	3 7	0 16	$p<0\ 05$

N S no statistical significance

(those who started on placebo and those who started on metoprolol) in Fig 2 Five women had BP≥160/95 and five women ≤140/90 in the seated position on placebo compared to two and nine respectively on metoprolol

Serum cholesterol and serum triglycerides (non fasting values) were determined at the end of the placebo and metoprolol periods of the cross-over study No significant differences were found for serum cholesterol (mean on placebo 274 mg/100 ml S E 5 9 mean on metoprolol 269 mg/100 ml S E 5 6) or for serum triglycerides (mean on placebo 1 6 mmole/l S E 0 12 mean on metoprolol 1 5 mmole/l S E 0 15) No abnormal values were found for Hb hematocrit leucocytes thrombocytes serum bilirubin alkaline phosphatases SGOT or SGPT One woman with diabetes mellitus continued to lose the same amount of protein and glucose in the urine as before the study apart from this patient neither proteinuria nor glucosuria was found

Side effects were few and benign One patient complained of dizziness and one of headache during the first few days when taking metoprolol and two patients also complained of difficulty in swallowing the tablets Three patients complained of slight headache during the first few days when taking placebo and one complained of chest pain after swallowing the placebo tablets

The patients were instructed to return the tablets remaining after the study had been completed and in this way it was calculated that 96% (range 80–100) of the placebo tablets and 95% (range 71–100) of the metoprolol tablets had been taken

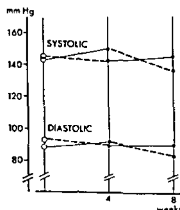


Fig 2 Systolic and diastolic blood pressures in the seated position during treatment with alprenolol (O) placebo (–) and metoprolol ( )

Comparison between metoprolol and previous alprenolol treatment

BP values recorded on metoprolol were similar to those recorded at the last clinical examination on alprenolol (Fig 2) Two women had BP ≥160/95 in the seated position both on alprenolol and metoprolol while three women had BP ≤140/90 on alprenolol compared to nine on metoprolol

Table III *Blood pressure heart rate body weight and serum uric acid after four weeks on different or unchanged doses of metoprolol*

	Period I		Period II		Significance of difference
	Mean	S E	Mean	S E	
Women on doubled metoprolol dose (n=9)					
Dose (mg t i d)	40		80		
Systolic BP (mmHg)					
Seated	150	6 1	148	5 5	N S
Supine	158	6 0	153	6 0	N S
Standing	156	7 0	152	4 0	N S
Diastolic BP phase 4 (mmHg)					
Seated	92	2 1	87	2 1	$p<0\ 05$
Supine	93	2 2	92	1 8	N S
Standing	97	1 6	92	2 2	N S
HR seated (beats/min)	68	2 8	64	2 9	N S ($p<0\ 1$)
B wt (kg)	76 9	6 9	76 1	6 7	N S
Serum uric acid (mg/100 ml)	3 9	0 2	4 1	0 3	N S
Women on unchanged metoprolol dose (n=15)					
Dose (mg t i d)	40		40		
Systolic BP (mmHg)					
Seated	134	3 0	134	3 5	N S
Supine	135	1 8	138	3 2	N S
Standing	140	3 1	137	3 0	N S
Diastolic BP phase 4 (mmHg)					
Seated	84	1 7	82	1 2	N S
Supine	85	1 5	84	1 5	N S
Standing	91	1 5	89	1 7	N S
HR seated (beats/min)	63	1 7	62	2 4	N S
B wt (kg)	71 9	4 3	71 7	4 3	N S
rum uric acid (mg/100 ml)	–	–	–	–	–

S =no statistical significance

Comparison between different doses of metoprolol

Table III compares the values recorded during treatment with 40 mg metoprolol t i d and 80 mg t i d in nine patients who had their dose doubled Values recorded in 15 women in whom no change of *the metoprolol dose was made after the cross-over* study are also shown in Table III There was a slight further but usually insignificant decrease in BP during treatment with the larger dose and a similar tendency was found for HR ($p<0\ 1$)

Follow up study on metoprolol

In Table IV BP HR body weight and serum uric acid values are presented for 23 patients who attended the four clinical examinations during the *follow up period As may be seen from the Table* these variables remained essentially unchanged when the metoprolol dose was unchanged Reduction of the amount given from 50 or 100 mg t i d to 50 or 100 mg b i d seemed to have a negligible influence on BP At the last clinical examination on the t i d regimen one woman had BP≥160/95 and 11 women had BP≤140/90 in the seated position compared to none and six respec tively on the b i d regimen

DISCUSSION

The patients who were admitted to the study had previously taken alprenolol and propranolol during separate periods with no or only slight transient

Table IV *Long term follow up on metoprolol (n = 23)*

	Administered t i d								Administered b i d			
	Oct or Nov 1972		April or June 1973[a]		Sept 1973		Jan 1974		May 1974		Oct 1974	
	Mean	S E	Mean	S E	Mean	S E	Mean	S E	Mean	S E	Mean	S E
Systolic BP (mmHg)												
Seated	141	3 4	141	2 4	138	3 2	136	4 3	141	2 7	141	2 8
Supine	143	3 5	144	3 0	140	3 2	141	3 9	145	2 7	149	2 8
Standing	146	3 5	144	2 5	144	2 7	140	3 8	145	2 5	150	2 5
Diastolic BP phase 4 (mmHg)												
Seated	87	1 6	86	1 2	83	1 4	85	1 6	88	1 4	87	1 3
Supine	88	1 5	88	1 2	85	1 4	87	1 7	88	1 4	88	1 3
Standing	93	1 2	93	1 3	93	1 3	91	1 4	94	1 2	92	1 4
HR seated (beats/min)	65	1 6	60	1 5	60	1 8	60	1 4	61	1 5	62	2 0
B wt (kg)	74 3	3 8	72 7	3 7	72 9	3 6	74 0	3 6	73 2	3 7	73 6	3 7
Serum uric acid (mg/100 ml)	3 7	0 16	3 8	0 2	–	–	3 8	0 16	–	–	4 0	0 2

[a] Nine patients doubled their metoprolol dose after the clinical examination in Nov 1972

side-effects As all the participants had previously taken β blocking agents the present patient material must be considered to be a selected one and does not permit detailed conclusions concerning side-effects in a non selected hypertensive population However it may be concluded that subjects who are taking other β blocking agents without side effects may without difficulty be changed over to metoprolol The occurrence of side-effects was similar during treatment with metoprolol and when on placebo both during the first few days and during a long term follow up period The side effects were benign and transient

Metoprolol reduced both the systolic and the diastolic BP significantly compared to placebo The differences in BP between the periods of metoprolol and placebo treatment are probably misleadingly low as a wash-out period of one month is too short to obtain pretreatment values after β blockers as had been shown earlier (2 15) BP was similar to that during a previous period on alprenolol and a subsequent double blind cross-over study comparing metoprolol and propranolol did not reveal any differences in antihypertensive effect between the two substances in this patient material either (5) When followed for about a year and a half BP remained at a similar level when the dose of metoprolol was unchanged

In other studies it has been found that the plasma half life of metoprolol is about four hours (7 11 14) Regårdh et al (14) also found that the effect of 100 mg metoprolol on the exercise HR was reduced to half the maximum value after about 8 hours Due to its long duration metoprolol was also administered twice daily in the present follow up study As the BP was well controlled in all the patients the daily dose of metoprolol was reduced in the b i d dosage regimen study The patients who had previously received 50 mg t i d now received 50 mg b i d and a corresponding reduction was made for the other patients so that 100 mg t i d was reduced to 100 mg b i d No or very slight differences in BP were noted when the number of administrations and the daily dose were reduced (Table IV) Consequently the drug may be administered twice daily at least after an initial period of treatment with a t i d regimen A b i d regimen must be considered as more convenient for the patient and less tablet failure may be expected on this regimen (2)

The HR was insignificantly lower during treatment with metoprolol than with alprenolol ($p < 0.1$) and similar to that when taking propranolol (5) while body weight was unchanged This trend towards a difference between alprenolol on the one hand and metoprolol and propranolol on the other is probably due to the intrinsic activity which alprenolol possesses (9)

Serum uric acid was slightly but significantly raised during metoprolol treatment compared to

placebo However this rise seemed to be of no clinical significance and there were no individual serum uric acid values ≥6 mg/100 ml A similar increase in serum uric acid has also been recorded after alprenolol (2) but this disappeared after a longer period of treatment with this drug (4) Alprenolol and propranolol seem to have equal effects in this respect (3)

The study did not indicate any influence on serum lipids Blood for serum lipid determination was not drawn in the fasting state but the conditions were identical when blood sampling was performed during the placebo period and the metoprolol period

In conclusion metoprolol seems to be a potent hypertensive agent and no serious or consistent side effects were noted in this series of hypertensive women followed up for more than two years It seemed that a b i d dosage regimen is sufficient and therefore is to be preferred

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Comparison between Metoprolol and Propranolol as Antihypertensive Agents

A Double blind Cross over Study

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ABSTRACT A new selective β adrenergic blocking agent—metoprolol—is compared to a non selective β adrenergic blocking agent—propranolol—according to a double blind cross-over technique in 23 hypertensive women who had previously taken alprenolol and propranolol during different periods No significant differences were found for blood pressure, heart rate, body weight or serum uric acid No side-effects which could be related to the therapy were seen with either drug

Metoprolol is a new selective adrenergic β_1 receptor blocking agent (3 10) which has been shown to reduce the blood pressure (BP) significantly compared to placebo and also to maintain the BP at a low value during a long term follow up (7) As part of the research programme for this substance metoprolol has been compared to propranolol in a double blind cross over study The substances were given in doses which had been shown to reduce exercise tachycardia to the same extent (11)

MATERIAL

The subjects were recruited from a material of 26 women who had previously participated in a trial comparing alprenolol and propranolol (6) Twenty four women aged 50-64 years (mean 56) when admitted were included in the study and 23 completed it One woman was excluded due to disease not related to her hypertension or antihypertensive treatment Except for one woman who had experienced breathlessness on moderate exertion none had a history or signs of cardiac or renal insufficiency They were all classified as grade 1-2 according to WHO s classification of hypertension None had severe eye ground changes One woman was classified as FH 0 according to Keith Wagener Barker the others as FH I-II

METHODS

Fig 1 shows the design of the study After a run in period of eight weeks during which the participants received placebo they were randomly allocated to metoprolol or propranolol as first active drug The drugs were given double blind and cross-over Each period lasted for eight weeks the total time for the study including the run in placebo period being 24 weeks All participants started and completed the trial at about the same time

The subjects underwent physical examination before and after the run in period and at the end of the placebo and treatment periods BP was measured after about 10 min rest with the patient in the seated supine and standing positions by the same examiner using a mercury sphygmomanometer as described previously (5) Heart rate (HR) was measured with the patient in the seated position Bilirubin SGOT SGPT alkaline phosphatases and serum uric acid were determined at the Central Laboratory of this hospital Serum uric acid was recorded according to an enzymatic method

Fifty mg of metoprolol tartrate was considered equipotent to 40 mg of propranolol hydrochloride (11) According to previous individual titration the patients received 50 mg or 100 mg of metoprolol t i d and 40 mg or 80 mg of propranolol t i d during the treatment periods The same number of tablets was also prescribed during the run in period Of those who completed the study eight received the higher dose and 15 the lower Twelve women were given metoprolol as the first active drug and 11 started with propranolol

The placebo tablets and the tablets containing active drug were of the same appearance and taste as the metoprolol tablets which they had taken previously The metoprolol and propranolol tablets had the same dissolution rate in vitro No special information was given when the placebo period was started During the treatment periods the women were informed that they were to receive two similar drugs in order to find out which one was the best for them

Statistical methods Data from the clinical controls were collected according to a special schedule There were no missing data The significance of difference between

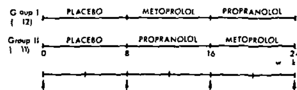


Fig 1 Design of the study Arrows denote clinical examinations

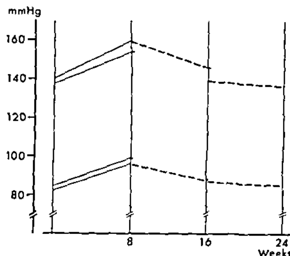


Fig 2 Systolic and diastolic blood pressures in the seated position during treatment with placebo (—) metoprolol ( ) and propranolol ( )

sample means was estimated by Student s *t* test for the means of differences between paired observations In this way each subject acted as her own control throughout the study The differences were considered statistically significant for $p<0\ 05$

RESULTS

Effects on arterial blood pressure

Mean values for BP in the seated supine and standing positions are shown in Fig 2 and in Table I Diastolic BP phase 5 is omitted in Table I as it closely followed phase 4 No significant differences were found between the two substances as may be seen from Fig 2 and also from Table I in which the total number of subjects on metoprolol or propranolol treatment is grouped together irrespective of whether starting on metoprolol or propranolol No fferences were found for individual values Thus the seated position no BPs≥160/95 were re rded on either drug Nine women had BPs≤ 140/90 on metoprolol and ten on propranolol

Effects on heart rate

No significant differences were found between metoprolol and propranolol concerning the effect on HR as may be seen from Table I The range during metoprolol treatment was 48–70 and during propranolol treatment 50–74 beats/min

Effects on body weight

No significant difference in body weight was found between metoprolol and propranolol as may be seen from Table I

Table I *Blood pressure heart rate body weight and serum uric acid after 8 weeks treatment with metoprolol and propranolol (n=23)*

	Metoprolol		Propranolol		Significance of difference
	Mean	S E	Mean	S E	
Systolic BP (mmHg)					
Seated	141	2 4	139	3 6	N S
Supine	144	3 0	146	3 7	N S
Standing	144	2 5	146	2 6	N S
Diastolic BP phase 4 (mmHg)					
Seated	86	1 2	86	1 2	N S
Supine	88	1 2	89	1 2	N S
Standing	93	1 3	94	1 2	N S
HR (beats/min)	59	1 5	62	1 4	N S
B wt (kg)	72 7	3 7	73 1	3 6	N S
Serum uric acid (mg/100 ml)	3 8	0 2	3 9	0 2	N S

N S = no statistical significance

Effects on laboratory data

Serum uric acid levels were similar during metoprolol and propranolol treatment (Table I) No high individual values were found either for metoprolol or for propranolol (none≥6 0 mg/100 ml)

Other laboratory data such as Hb hematocrit bilirubin alkaline phosphatases SGOT SGPT leukocytes and thrombocytes remained within normal limits One woman with mild proteinuria before the study continued to lose the same amount of protein in the urine during both treatment periods as before the cross-over study She also had mild diabetes mellitus with glucosuria which also remained unchanged

Side effects

Only one woman complained of side effects At the beginning of the metoprolol period she had symptoms of gastroenteritis including vomiting and could not take tablets for a few days Whether her symptoms were caused by metoprolol or not could not be determined Prior to the run in period she had taken 100 mg t i d without side effects When symptom free she continued to take 50 mg metoprolol or 40 mg propranolol t i d throughout the study and had no further symptoms

Control of tablet intake

By counting the tablets remaining after each treatment period it was calculated that 94% of the metoprolol tablets (range 75–100) and 96% of the propranolol tablets (range 74–100) had been taken

DISCUSSION

In the present investigation the systolic and diastolic BPs were reduced to the same extent after the β_1 selective drug metoprolol as after propranolol when given in equipotent β_1 receptor blocking doses This finding might indicate that the antihypertensive effect of the β blockers is mainly exerted via blockade of β_1 receptors This effect might however be modified by a β_2 receptor blocking action and by an intrinsic activity of different β blockers

As the patients in the present study had mild hypertension and had been treated with antihypertensive drugs for a couple of years with concomitant carry-over effect (5) it seems reasonable to assume that individual and minor differences in the antihypertensive effects of the two drugs are difficult to demonstrate in this patient material

In the present investigation metoprolol and propranolol were given in doses which had been found to reduce the exercise tachycardia in healthy volunteers to the same extent (11) It seems reasonable to assume that the two drugs also had equal effects on HR in the present study as the resting HR after the two drugs did not differ significantly Furthermore the two drugs probably had the same effects on cardiac output ($\dot{Q}$) as animal studies indicate that their respective effects on Q are parallel to their action on HR (2) A decrease in Q is undoubtedly of great importance for the antihypertensive action of β-blockers However although almost all patients have a reduced $\dot{Q}$ only those who also have a reduced or unchanged vascular peripheral resistance exhibit a good antihypertensive response to β blockers (9 14)

Other actions of the β blockers might contribute to their antihypertensive effect There is still controversy concerning what significance any action of the drugs on the secretion of renin has for their antihypertensive effect Recently it has been shown that metoprolol might affect the release of renin to a similar degree as propranolol (4) Other effects which might be of importance for the hypotensive action of these drugs include adrenergic neuron blockade (1) and central nervous action (13) The relative importance of these effects for their antihypertensive action remains to be established and furthermore it is not known whether these effects are mediated via β_1 or β_2 receptors or via other types of receptors

Both metoprolol and propranolol were well tolerated in the present investigation and there were no significant differences in the laboratory variables after the two drugs Only a few side effects of transient character were reported the number being similar to that with placebo (7)

A great difference between metoprolol and propranolol regarding side effects may be expected in patients with asthma and chronic bronchitis It has been shown that the effect of isoprenaline on forced expiratory volume in one second in asthmatics is blocked to a considerably greater extent by propranolol than by metoprolol (12) Moreover, patients who suffer from hypertension and are on β_2-stimulators due to asthma, have been treated with metoprolol without any change for the worse in their bronchial function (8)

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Enzymes and Long-term Survival after First Myocardial Infarction

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ABSTRACT The study covers 342 patients still alive one month after the acute attack of their first myocardial infarction Daily determinations of creatinine phosphokinase (CPK) lactic dehydrogenase (LDH) and glutamic oxaloacetic transaminase (SGOT) in serum were carried out during hospitalization so that a maximum enzyme value could be obtained for each enzyme and patient A follow up examination was performed after an observation time ranging from 12 to 38 months Having calculated the mean (x) of the maximum enzyme values a parallel relationship was found between the maximum CPK LDH and SGOT values and the long term prognosis in myocardial infarction inasmuch as patients with maximum enzyme values above or equal to the mean had a significantly higher 2 year mortality than patients with values below x In order to detect any slight difference between the three enzymes with reference to the long-term prognosis, the material was divided into four groups one with peak values less than $x-x/2$ (lowest), one with values from $x-x/2$ to x exclusive (next lowest) one with values from x to $x+x/2$ exclusive (next highest) and a group with peak elevations greater than or equal to $x+x/2$ (highest) A tendency to increasing mortality from the next lowest to the highest maximum enzyme values was found On the other hand, patients with the lowest peak values had a tendency to higher mortality than patients in the next lowest group This characteristic was observed with regard to both CPK and LDH and to some extent to SGOT

The size of the infarction and the functional capacity of the remaining myocardium are important factors for the prognosis when evaluating the long term survival following acute myocardial infarction (AMI)

As a number of investigations (7 8 13 15 21) have shown that there is a positive correlation between maximum enzyme values of lactic dehydrogenase (LDH) glutamic oxaloacetic transaminase (SGOT) in serum and the size of a myocardial infarction one would expect the maximum enzyme values to yield information as to the long term prognosis in AMI The few studies which have been carried out to date (6 10 12 13) have on the whole confirmed this assumption but the results are somewhat ambiguous besides being difficult to compare owing to the use of different enzyme units and in some cases comprising only a small number of patients The relationship between serum creatinine phosphokinase (CPK) and long term survival in AMI has apparently not been studied before

The object of the present study has been on the basis of a reasonably large material to evaluate both the relationship between maximum values of CPK LDH and SGOT and long term survival following AMI and also the importance of the three enzymes as indicators of the long term prognosis

MATERIAL AND METHODS

The study covers 263 men and 79 women who had been admitted to the Coronary Care Unit (CCU) of the University Hospital of Odense from Nov 1969 to Dec 1971 All had AMI according to the following definitions precordial pain of long duration and/or acute pulmonary edema in connection with the occurrence of signs of infarction on ECG and/or characteristic increase in enzymes In addition the following criteria were fulfilled by all patients 1) first myocardial infarction 2) admission to the CCU within 24 hours of the onset of symptoms 3) survival after the acute phase (days 0–30 inclusive)

Enzyme analysis

Blood samples for enzyme analysis were drawn from the majority of patients immediately after admission The analysis was carried out depending upon the time of admission either immediately after sa[illegible] or

Table I *The day following admission on which enzyme values reached a maximum*

Enzyme (U/l)	Day 1	2	3	4	5	≥6
CPK	58	220	53	7	2	2
LDH	13	69	192	53	10	5
SGOT	39	194	87	9	7	6

next routine analysis (on serum stored at 4 C) In the following days the blood samples were taken between 7 30 and 10 00 and the analysis was carried out immediately

In the study period the CPK analyses were carried out manually according to a modification of the method of Tanzer and Gilvarg (20) The variation coefficient (1 daily control for 10 months) was 9 1% The normal range for men was 1 0-8 2 U/l and for women 0 9-4 4 U/l

The LDH determinations were carried out using the Autochemist according to a colorimetric method (2) The variation coefficient (6 controls daily for 5 months) was 3 7% and the normal range 98-216 U/l

SGOT values were determined by autoanalytic technic (Autochemist) according to a colorimetric method (9 18) The variation coefficient (6 controls daily for 5 months) was 3% The normal range was 2-15 U/l

Daily estimations of CPK LDH and SGOT values were carried out in the majority of patients until normal values were obtained Thus a peak value for each of the three enzymes could be obtained for every patient Table I shows the day with maximum enzyme values

Maximum enzyme values were used in the following ions No significant difference was found between maximum enzyme values in men and women or be younger and older patients (17) Thus no allowance as been made in the calculations for age or sex

Follow up

The patients were followed up on Jan 1st 1973 The minimum period of observation was 12 months the maximum 38 months Information regarding the patients was

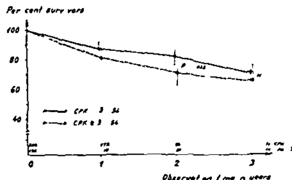


Fig 1 Survival curves of patients alive one month after first myocardial infarction according to maximum values of CPK

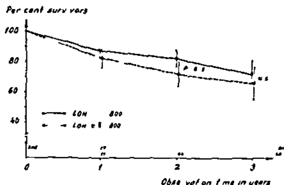


Fig 2 Survival curves of patients alive one month after first myocardial infarction according to maximum values of LDH

obtained from hospital records National Registration Offices general practitioners Medical Officers of Health and the Central Register of Deaths of the National Health Service

Of the 342 patients 339 were traced The remaining 3 were foreigners who had been visiting this country all three were discharged alive

Statistical analysis

The actuarial method has been employed in the calculation of survival probability (3) Confidence limits of 95% have been used in the survival curves The standard deviation has been calculated with the Greenwood s estimate Statistical comparison between the survival rates has been carried out partly by evaluation of the curves with safety intervals and partly using the $2 \times n \chi^2$ test where n is the number of observation intervals (1) For $p<0.05$ the difference has been considered significant

RESULTS

The mean (x) of the maximum CPK values in 342 patients was 54 U/l Peak CPK values below x were found in 206 patients while 136 had peak elevations greater than or equal to x The survival curves for these two patient groups are shown in Fig 1 The number of patients alive at the beginning of each observation period is indicated in the Figure by lx Patients with a maximum CPK value above or equal to x had a significantly lower 2 year survival than patients with a peak CPK activity below x but after 3 years of observation there was no significant difference in the survival rates

The mean of the maximum LDH values was 800 U/l Peak LDH elevations below and above x were found in 205 and 137 patients respectively As will be seen from Fig 2 the 2 year survival rate was significantly lower for patients with a peak LDH activity above or equal to x than for patients with

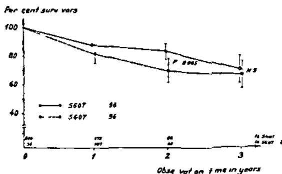


Fig 3 Survival curves of patients alive one month after first myocardial infarction according to maximum values of SGOT

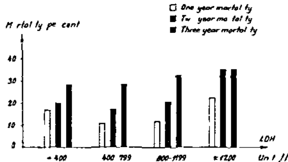


Fig 5 Mortality among patients alive one month after first myocardial infarction according to maximum LDH values

maximum LDH levels below $\bar{x}$ whereas there was no significant difference in the 3 year survival rates

The mean of the maximum SGOT values was 96 U/l 206 and 136 patients had peak SGOT elevations below and above $\bar{x}$ respectively The 2 year surviv al for patients with peak SGOT values above or equal to $\bar{x}$ was significantly lower than that for pa tients with maximum SGOT levels below $\bar{x}$ There was no significant difference in the 3 year survival as can be seen from Fig 3

The material was also divided into groups on the basis of the peak values inasmuch as $\bar{x}/2$ was either subtracted or added to $\bar{x}$ thus making it possible to operate with four patient groups one with max imum activity less than $\bar{x}-\bar{x}/2$ (lowest) one with values from $\bar{x}-\bar{x}/2$ to $\bar{x}$ exclusive (next lowest) one with values from $\bar{x}$ to $\bar{x}+\bar{x}/2$ exclusive (next highest) and a group with peak elevations greater than or equal to $\bar{x}+\bar{x}/2$ (highest) The cumulative 1 2 and 3 year survival has been calculated for each group and the corresponding mortality is shown in Figs 4–6

Fig 4 shows the mortality with regard to CPK using this grouping Patients with the lowest max imum CPK activity had an insignificantly higher mortality than those with the next lowest values but from this group upwards there was a tendency to increasing mortality

The same pattern was found with regard to LDH as can be seen from Fig 5—an insignificantly higher mortality in the lowest enzyme group than in the next lowest and from there upwards an increasing mortality with increasing maximum LDH values

With regard to SGOT there was some tendency to a higher 1 and 2 year mortality in the lowest enzyme group as compared to the next lowest whereas the 3 year mortality showed the reverse tendency as can be seen from Fig 6 Apart from the 3 year mortality in the next lowest group and the 2 year mortality in the next highest group there was a tendency to increasing mortality with increasing peak values from the next lowest SGOT enzyme group to the highest

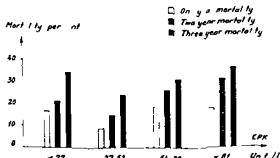


Fig 4 Mortality among patients alive one month after first myocardial infarction according to maximum CPK values

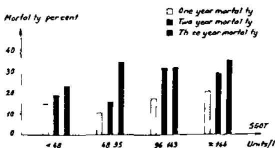


Fig 6 Mortality among patients alive one month after first myocardial infarction according to maximum SGOT values

Table I. *The day following admission on which enzyme values reached a maximum*

Enzyme (U/l)	Day 1	2	3	4	5	≥6
CPK	58	220	53	7	2	2
LDH	13	69	192	53	10	5
SGOT	39	194	87	9	7	6

next routine analysis (on serum stored at 4 C). In the following days the blood samples were taken between 7.30 and 10.00 and the analysis was carried out immediately.

In the study period the CPK analyses were carried out manually according to a modification of the method of Tanzer and Gilvarg (20). The variation coefficient (1 daily control for 10 months) was 9.1%. The normal range for men was 1.0–8.2 U/l and for women 0.9–4.4 U/l.

The LDH determinations were carried out using the "Autochemist" according to a colorimetric method (7). The variation coefficient (6 controls daily for 5 months) was 3.7% and the normal range 98–216 U/l.

SGOT values were determined by autoanalytic technic ("Autochemist") according to a colorimetric method (9, 18). The variation coefficient (6 controls daily for 5 months) was 3%. The normal range was 2–15 U/l.

Daily estimations of CPK, LDH and SGOT values were carried out in the majority of patients until normal values were obtained. Thus a peak value for each of the three enzymes could be obtained for every patient. Table I shows the day with maximum enzyme values.

Maximum enzyme values were used in the following calculations. No significant difference was found between the maximum enzyme values in men and women or between younger and older patients (17). Thus no allowance has been made in the calculations for age or sex.

Follow up

The patients were followed up on Jan. 1st 1973. The minimum period of observation was 12 months, the maximum 38 months. Information regarding the patients was obtained from hospital records, National Registration Offices, general practitioners, Medical Officers of Health and the Central Register of Deaths of the National Health Service.

Of the 342 patients, 339 were traced. The remaining 3 were foreigners who had been visiting this country; all three were discharged alive.

Statistical analysis

The actuarial method has been employed in the calculation of survival probability (3). Confidence limits of 95% have been used in the survival curves. The standard deviation has been calculated with the "Greenwood's estimate". Statistical comparison between the survival rates has been carried out partly by evaluation of the curves with safety intervals and partly using the $2 \times n\chi^2$ test where n is the number of observation intervals (1). For $p < 0.05$ the difference has been considered significant.

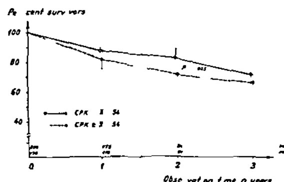


Fig. 1. Survival curves of patients alive one month after first myocardial infarction according to maximum values of CPK.

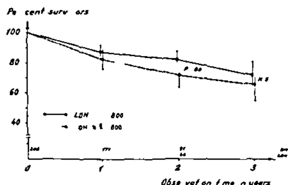


Fig. 2. Survival curves of patients alive one month after first myocardial infarction according to maximum values of LDH.

RESULTS

The mean ($\bar{x}$) of the maximum CPK values in 342 patients was 54 U/l. Peak CPK values below $\bar{x}$ were found in 206 patients, while 136 had peak elevations greater than or equal to $\bar{x}$. The survival curves for these two patient groups are shown in Fig. 1. The number of patients alive at the beginning of each observation period is indicated in the Figure by l_x. Patients with a maximum CPK value above or equal to $\bar{x}$ had a significantly lower 2 year survival than patients with a peak CPK activity below $\bar{x}$, but after 3 years of observation there was no significant difference in the survival rates.

The mean of the maximum LDH values was 800 U/l. Peak LDH elevations below and above $\bar{x}$ were found in 205 and 137 patients, respectively. As will be seen from Fig. 2, the 2 year survival rate was significantly lower for patients with a peak LDH activity above or equal to $\bar{x}$ than for patients with

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DISCUSSION

Infarct size is a major determinant of the prognosis after AMI (19). A quantitative measure of the infarction size can be obtained by analyzing serial serum CPK changes after the acute attack (19). It has in addition been demonstrated in experimental and clinicopathological studies that there is also a positive correlation between peak levels of serum enzymes such as LDH and SGOT and the size of the infarction (7, 8, 13, 15, 21). A number of clinical studies have shown that high maximum enzyme activities of CPK, LDH and SGOT are synonymous with a poor immediate prognosis in AMI (4, 5, 10, 11, 13, 16). Long term prognosis in relation to peak enzyme levels has been studied only in a few investigations, all from Sweden, and mostly with regard to SGOT. Two studies (6, 10) revealed a tendency to a higher 1 year mortality with high maximum SGOT values, whereas Hofvendahl (12) found no significant difference in the 1 year mortality between various maximum SGOT activities. Helmers (10) found a tendency to increased 3 year mortality with high maximum SGOT values. Kibe and Nilsson (13) observed a significantly increased 2 and 5 year mortality with high maximum LDH and SGOT activities, however, in this study there were not many patients with high maximum enzyme values.

It appears that CPK has not been investigated ... regard to the relationship between peak en... levels and long term prognosis. The results of ...ese long term prognosis studies are difficult to compare, partly because different enzyme units are used in the different hospitals and partly owing to the choice of different enzyme intervals when grouping the patients. In order to avoid this complication, the mean of the maximum enzyme elevations has been employed in the present study as the starting point for the subgrouping. Thus the present material can be compared to others grouped similarly, regardless of the choice of units.

A parallel relationship was found between CPK, LDH and SGOT and the long term prognosis in AMI, inasmuch as patients with maximum enzyme values above or equal to the mean figure of all three enzymes had a significantly higher 2 year mortality than those with peak levels below this figure, whereas there was no significant difference in the 3 year mortality. However, only a few patients had been under observation for a full three years, which introduces some uncertainty to the conclusions based on comparisons between the 3 year survival groups.

In order to determine whether or not there was some slight difference with regard to the long term prognosis between the three enzymes, a uniform subgrouping was employed based on the mean value. There was a tendency for mortality to increase from the next lowest to the highest maximum enzyme activities. This applied to CPK and LDH and to some degree to SGOT. In the group with the lowest values there was an insignificantly higher mortality than in the next lowest group, apart from the 3 year mortality with regard to SGOT. However, Helmers (10) has demonstrated a tendency to a higher 3 year mortality in patients with the lowest maximum SGOT values. The fact that the mortality with regard to SGOT differs somewhat from that according to CPK and LDH might be connected with more falsely high SGOT values as a result of congestive heart failure.

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Is Streptokinase Useful in the Treatment of Deep Vein Thrombosis?

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ABSTRACT Because of its fibrinolytic action streptokinase is believed to reduce the severity of the postthrombotic syndrome in patients with deep vein thrombosis A prospective and a retrospective study have been undertaken in an attempt to determine when this therapy is useful for patients with deep vein thrombosis The prospective study included 15 patients with deep vein thrombosis 5 were treated in the hospital with streptokinase and heparin and 5 only with heparin, 5 were treated at home with only phenprocoumon All the patients received oral anticoagulant therapy for at least 6 months Three to four months after the acute episode, phlebography and venous pressure measurements were carried out Streptokinase appeared to give the best results but with more side effects In the retrospective study 51 patients who had had deep vein thrombosis in 1969 were reexamined 31–47 months later It was found that more than 50% of the patients with a thrombosis in the femoral and/or iliac vein developed a severe postthrombotic syndrome in contrast to only 9% of those with a thrombosis in the popliteal vein or lower It is recommended on the basis of both the prospective and the retrospective study that patients with a thrombosis in the femoral and/or iliac vein should be treated with either heparin or streptokinase during the early stage It is probable that streptokinase will significantly decrease the frequency and severity of the postthrombotic syndrome in these patients in particular although this has not yet been proven

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Pulmonary embolism is the most feared complication of deep vein thrombosis although this risk is considerably reduced by anticoagulant therapy (18) Another complication which can develop after venous thrombosis is the postthrombotic syndrome Before the introduction of anticoagulant therapy most patients with venous thrombosis developed this syndrome (2) it has since been shown that anticoagulants reduce its severity and frequency (2 4 23)

Thrombolytic therapy for deep vein thrombosis has been discussed in a number of recent publications (6 8 11 13 14 16 17 19 22) Although thrombolytic agents do not reduce the risk of pulmonary embolism it has been postulated that dissolution and breakdown of the thrombus will preserve the venous valves which should prevent the postthrombotic syndrome A good comparative study of thrombolytic versus conventional antithrombotic treatment for the prevention of the postthrombotic syndrome has not yet been described The lack of recent data from follow up studies of patients with deep vein thrombosis treated with anticoagulants makes it difficult to assess the value of introducing a new form of treatment for prevention of the postthrombotic syndrome

The purpose of our investigation was to determine the usefulness of treating deep vein thrombosis with streptokinase We approached this problem from two directions (*a*) A prospective study In a controlled clinical trial two groups of patients received antithrombotic treatment with oral anticoagulants initiated in the hospital with either streptokinase followed by heparin (streptokinase group) or with heparin alone (heparin group)—A

third group of patients received only phenprocoumon and was treated from the beginning at home (phenprocoumon group) (*b*) A retrospective study We determined which patients with deep vein thrombosis in 1969 developed a severe post thrombotic syndrome

PATIENTS AND METHODS

Prospective Study

Each of the three groups in the prospective study consisted of five patients Those admitted to the hospital took part in the controlled clinical trial The patients treated at home could not be randomized because the decision to treat at home with only phenprocoumon was made by the general practitioner

Controlled trial (patients treated in hospital)

Criteria for admission to the trial All patients with the diagnosis venous thrombosis of the leg with or without pulmonary embolism were included in the study if they satisfied the following requirements

(*a*) The diagnosis of venous thrombosis had to be made independently by at least two physicians The minimal criteria were acute swelling of the affected leg whereby the circumference of the calf had to be at least 1 5 cm more than that of the normal leg pain in the affected leg in the form of tenderness of the calf on palpation positive Homan s sign or local pain over the thrombosed veins (*b*) The interval between the first symptom of pain and edema and the initiation of therapy had to be less than 120 hours (*c*) The patient had to be 65 years or younger ; No past history of thromboembolism (*e*) Patients re excluded from the study in the event of hemorrhagic hesis surgery during the preceding 7 days hyper on with a diastolic pressure above 120 mmHg or with Keith Wagener grade III or IV retinopathy bleeding lesion in the digestive or urogenital tract a severe renal or hepatic insufficiency bacterial endocarditis atrial fibrillation or pregnancy Patients with a poor prognosis previous cerebrovascular accident invalidity (paralysis amputation etc) extensive varicosis effective therapy with coumarin drugs or recent streptococcal infections were also excluded from the study

Randomization If the patient was accepted for the study the therapy to be followed was determined by the statistician who provided consecutive series of 10 sealed envelopes to be used in sequence In the group of 10 patients five were treated with heparin and five with streptokinase

Therapy Bed rest was prescribed for all patients the foot of the bed was elevated Mobilization was started as soon as the temperature was normal the acute symptoms of venous thrombosis had disappeared and oral anticoagulant therapy with phenprocoumon was effective In any event mobilization had to begin within one week unless contraindicated During mobilization the affected leg was bandaged

Each patient received 25 mg prednisolone (Di adreson F®) before therapy was started and on the next two days this was done to prevent the side effects of the streptokinase therapy Streptokinase (Streptase®) was administered as a continuous infusion via an infusion pump into a superficial vein of the arm for 72 hours An initial loading dose of 250 000 U was given in 30 min followed by a maintenance dose of 100 000 U/hour The streptokinase infusion could be discontinued in the event of severe bleeding or other serious side effects If the thrombin time was not prolonged at least two times after 48 hours heparin (Thromboliquine®) 25 000 U/24 hours was also administered in a continuous infusion In any case two hours after discontinuation of streptokinase a continuous infusion of 20 000 U heparin/24 hours was started the dosage was adjusted to keep the recalcification time between 6 and 10 min (normal<5) This therapy was continued until oral anticoagulation with phenprocoumon was effective the latter was started at the end of the second day

The control group received conventional anticoagulant therapy with phenprocoumon in combination with i v heparin injections The initial heparin dose was 15 000 U i v every six hours the next day the heparin dose was adjusted as required to keep the recalcification time between 6 and 10 min just before the next heparin injection Administration of heparin was discontinued as soon as anticoagulant therapy with phenprocoumon was effective

Oral anticoagulant therapy was continued in all patients for at least 6 months Supervision was carried out by the Thrombosis Service the Thrombotest according to Owren (15) was used Oral anticoagulant therapy was considered well adjusted and effective when the Thrombotest values were between 5 and 10 %

During the first four days the following laboratory examinations were carried out daily hematocrit Thrombotest time recalcification and thrombin times according to the methods described by Veltkamp et al (20) and the fibrinogen determination according to Clauss (5) In addition platelet counts were checked regularly according to the method of Feissly and Lüdin (7)

Assessment of progress (*a*) *Clinical* The patients were examined daily and the following aspects of the leg were noted tenderness circumference of both legs at various levels color temperature difference and dilatation of superficial veins After discharge the patients were also checked regularly in the Outpatient Clinic A clinical differentiation was made between thrombosis of the upper and the lower leg A thrombosis of the upper leg is understood to mean a thrombotic occlusion of the femoral and/or iliac vein whereby the entire leg is edematous In thrombosis of the lower leg edema is restricted to the lower leg and the thrombotic occlusion is in the popliteal vein or lower

The severity of the postthrombotic syndrome was classified as follows 0=no complaints or abnormalities 1=only complaints of fatigue or tenderness 2=swelling after exertion or minimal chronic edema 3=chronic swelling of the leg 4=discoloration or induration of the skin leg ulcers

(*b*) *Phlebography and venous pressure measurements* Three or four months after the occurrence of venous thrombosis phlebography and venous pressure measure

ments were carried out in the Outpatient Clinic in both legs (the normal leg served as control for the affected leg) according to the method described by Van der Heyde (10) An ascending phlebogram was made the contrast medium was injected via a polythene catheter inserted by a cut down in a vein between metatarsal I and II The patient stood erect and a tourniquet was always placed around the ankle Exposures were made under television control in several directions by rotating the leg Movement of the feet and Valsalva s maneuver were usually sufficient to ensure good phlebograms

For the venous pressure measurements the same vein was used The polythene catheter was then connected via a 3 way cock to a graduated tube which gave the pressure in cm The system was refilled from a syringe containing physiologic saline solution

The following measurements were made SVP standing venous pressure after the patient has stood quietly for several minutes WVP_1 walking venous pressure the patient performs walking motions while remaining in place The resulting drop in pressure is measured and recorded WVP_2 WVP_1 with tourniquet below the knee which eliminates the influence of incompetence of the great saphenous veins and/or perforating veins of the upper leg WVP_3 WVP_1 with tourniquet around the ankle which eliminates the influence of incompetence of the great or small saphenous veins and/or perforating veins of the leg

The latter measurement (WVP_3) reflects the function of the venous pump undisturbed by incompetence of superficial and perforating veins With this method a decrease in the venous pressure of at least 50% is considered normal Use of the tourniquet below the knee or around the ankle made no difference in healthy individuals

The classification of the venous pressure determinations was as follows Normal if the ratio WVP_3 SVP was<50% Pathological if the ratio WVP_3 SVP was >50% but <80% Highly pathological if the ratio WVP_3 SVP was >80%

The phlebograms were evaluated by a vascular surgeon who did not know the site of thrombosis nor the therapy given One month later the thrombosis site and pressure measurement data were given to the same surgeon who then reevaluated the phlebograms The therapy used was still not known

Phenprocoumon group (patients treated at home)

In the Netherlands patients with deep vein thrombosis are treated not only in the hospital but also at home by the general practitioner The oral anticoagulant therapy is regulated by the Thrombosis Service During the trial we also visited all patients with deep vein thrombosis supervised at home by the Thrombosis Service in Leiden to see if any of these patients satisfied the criteria applied to the patients included in the trial If so and in consultation with the general practitioner pressure measurements and phlebography were carried out 3–4 months after the occurrence of the thrombosis This group was compared with the patients in the trial to see whether treatment at home is as effective as treatment in the hospital All patients treated at home who satisfied our criteria took part in this investigation The general practitioner regulated all further treatment such as elevation of the bed duration of immobilization and wearing bandages The patients received only phenprocoumon the duration of anticoagulant therapy was at least 6 months The patients were not given i v prednisolone

Retrospective Study

The Thrombosis Service in Leiden serves an area with about 380000 inhabitants All patients in this region who had had deep vein thrombosis in 1969 and were 65 years old or younger in 1972 qualified for this study The diagnosis of deep vein thrombosis of the leg was made by the general practitioner or a specialist If the diagnosis was dubious (no pain and/or edema) the patient was excluded For these patients too a differentiation was made between thrombosis of the upper and the lower leg For the severity of the postthrombotic syndrome the same classification was used as in the prospective study

RESULTS

Prospective Study

Early results

The clinical data for all patients as well as the complications due to the therapy given are listed in Table I The laboratory data are given in Table II and the follow up study with the results of the venous pressure measurements and phlebography in Table III In each group there were three patients with thrombosis of the upper leg and two with thrombosis of the lower leg None of the patients died

Heparin group All patients received 30000–100000 U heparin/day for four days After three days of phenprocoumon therapy a good oral anticoagulant effect was already noticeable (Table II) There was rapid clinical improvement especially with respect to pain the feeling of tightness in the leg and temperature difference At discharge two patients still had swelling of the leg (nos 1 and 9) leg size was however much smaller than on admission In one patient (no 9) pulmonary embolism occurred before initiation of therapy and during the first day of treatment there were no further complications

Streptokinase group All but two patients (nos 3 and 5) received streptokinase in the prescribed dose All showed a rapid clinical improvement with one exception (no 8) During the administration of streptokinase this patient experienced aggravation of pain with a definite increase in edema In contrast to the other patients the decrease in fibrino-

Table I *Clinical data for the 15 patients with deep vein thrombosis*

Case no	Sex	Age (y)	Predisposing factor	Site of thrombus	Interval between onset of symptoms and treatment (h)	Clinical result	Complications and side effects during treatment
Heparin group							
1	♀	51	Idiopathic	Upper leg L	24	Fair	
2	♂	58	Idiopathic	Lower leg L	36	Good	
4	♀	28	Oral contraceptive	Upper leg L	37	Good	
6	♂	64	Idiopathic	Lower leg L	11	Good	
9	♀	22	Oral contraceptive	Upper leg L	24	Reasonable	Pulmonary embolism on the first day
Streptokinase group							
3	♀	20	Postpartum	Lower leg R	20	Good	Headache backache vaginal bleeding many hematomas
5	♀	27	Oral contraceptive	Upper leg L	24	Good	Headache backache nausea fever bleeding from venepuncture sites hematomas
7	♀	34	Oral contraceptive	Upper leg R	48	Good	Hematomas macroscopic hematuria
8	♂	21	Trauma	Upper leg L	18	Poor	Elevated transaminases
10	♂	42	Idiopathic	Upper leg L	100	Good	Fever elevated transaminases
Phenprocoumon group							
11	♀	31	Oral contraceptive	Upper leg L	24	Poor	
12	♂	39	Idiopathic	Upper leg L	24	Poor	
13	♀	23	Postpartum	Upper leg L	48	Poor	
14	♀	54	Immobilization	Lower leg L	72	Poor	
15	♀	27	Postoperative	Lower leg R	72	Fair	

concentration and the prolongation of the in time were both insufficient (Table II) 48 hours when the thrombin time was 15 1 ... the patient received a continuous heparin infusion in addition to the streptokinase therapy At

Table II *Laboratory data for the 10 patients in the trial after 72 hour therapy*

Case no	Thrombotest (sec)	Thrombin time (sec)	Fibrinogen (mg/100 ml)
Heparin group			
1	130	>60	1 020
2	113	>60	450
4	185	>60	650
6	120	>60	680
9	157	17 7	690
Streptokinase group			
3*	46	34 9	21
5	55	33 5	32
7	52	28 5	45
8	72	15 1	200
10	74	27 2	70
Normal values	42	12	200–400

* After 48-hour streptokinase infusion

discharge the affected leg was still swollen The laboratory results for the other four patients showed a good fibrinolytic effect

Clinically three patients developed hemorrhagic diathesis The streptokinase infusion was discontinued prematurely in two cases (nos 3 and 5) for this reason in one case after 50 hours because of blood loss via the vagina in the other after 67 hours due to spontaneous hematomas In the latter patient the thrombin time 72 hours after initiation of the streptokinase infusion was still within the desired range Blood transfusions were not necessary As no patient had received acetylsalicylic acid or dextran interference with platelet function by these agents can be ruled out By chance the transaminase values in two patients were determined before during and after the administration of streptokinase and found to be transiently elevated Other side-effects observed with streptokinase were headache nausea abdominal pain and back pain (2 pats) fever (2 pats)

Phenprocoumon group (patients treated at home) In contrast to the two former groups clini

Table III *Follow up study of the 15 patients with the results of the venous pressure determinations and phlebogram*

Case no	Venous pressure	Phlebogram	Severity of the post thrombotic syndrome (grade) After 3 mo	After 12 mo
Heparin group				
1	Highly pathological	Extensive postthrombotic changes in all veins	3	3
2	Normal	Normal	0	0
4	Normal	Occlusion of distal third part of femoral vein	1	0
6	Pathological	Occlusion of proximal part of popliteal vein good collateral circulation	0	0
9	Highly pathological	Extensive postthrombotic changes in popliteal and femoral vein occlusion of proximal part of femoral vein	3	3
Streptokinase group				
3	Normal	Normal no filling of anterior and posterior tibial veins	1	0
5	Pathological	Normal	0	0
7	Normal	Normal	0	0
8	Pathological	Normal no functioning valves in popliteal and femoral veins	1	0
10	Normal	Normal no filling of anterior tibial and peroneal veins	0	0
Phenprocoumon group				
11	Pathological	Extensive postthrombotic changes in all veins	3	3
12	Highly pathological	No functioning valves except distally in the veins of the lower leg occlusion of common femoral vein?	3	3
13	Highly pathological	Extensive postthrombotic changes in all veins	3	3
14	Highly pathological	Occlusion of all veins of the lower leg popliteal vein recanalized	3	3
15	Normal	Normal	0	0

cal improvement of the five patients treated at home with phenprocoumon was very slow swelling sometimes persisted for weeks especially in thrombosis of the upper leg and relief from pain was only gradual None developed pulmonary embolism or bleeding

Late results

Follow up study (Table III) At the time of the follow up study all patients treated in the hospital were performing their normal work most of them had practically no complaints Measurements of the leg revealed only two patients (nos 1 and 9) with an obvious difference in leg size as a result of chronic edema this had already been noted at discharge from the hospital Effective oral anticoagulation could be continued after discharge in all patients In addition it also appeared that none of the patients treated at home were handicapped as a result of the thrombosis although four of the five patients (nos 11–14) had a severe postthrombotic syndrome 3–4 months later Oral anticoagulation was well regulated for all patients except patient 13 None of the patients with chronic edema (grade 3) three months after the occurrence of the thrombosis showed any improvement 12 months later

Results of phlebography and venous pressure measurements For almost all patients pressure measurements and phlebography were carried out in the normal and the affected leg In one patient (no 14) pressure measurement of the normal leg failed in two patients (nos 1 and 2) phlebography was not carried out in the normal leg There was no essential difference between the first (blind) and second (location of thrombosis and venous pressure determinations known) interpretations of the phlebograms by the vascular surgeon The results for the normal legs were all normal and are therefore not included in Table III (except the venous pressure determinations for the right leg in patient 12 the phlebogram of the deep veins was completely normal) All patients with thrombosis of the lower leg showed no or only slight abnormalities with the exception of patient 14 The patients with throm-

Table IV *Severity of the postthrombotic syndrome in 51 patients with deep venous thrombosis*

Severity grade	Site of thrombus		Total
	Upper leg	Lower leg	
0	2	13	15
1	3	9	12
2	2	10	12
3	7	2	9
4	2	1	3
Total	16	35	51

bosis of the upper leg showed more serious abnormalities although the results for the patients treated with streptokinase were much better There was good correlation with the clinical results the patients with a serious form of postthrombotic syndrome (i e grade 3) also showed the greatest abnormalities in venous pressure measurements and on the phlebograms

Retrospective Study

In 1969 146 patients in Leiden and the surrounding communities had deep vein thrombosis 89 of them were 65 years old or younger in 1972 This group was used for a follow up study 31–47 months had passed since the thrombosis had occurred For 21 of he 89 patients a follow up study was impossible use of death (15) complete immobilization or unavailability (4) To permit comparisons ith the prospective study patients with a past history of thromboembolism (17) were also excluded leaving 51 patients for the retrospective study

No differentiation was made between patients treated in the hospital or at home since half of the patients treated in hospital did not receive heparin The average duration of treatment with coumarin drugs was 3 months None of the patients were treated with streptokinase Table IV shows the results

More than half of the patients with thrombosis of the upper leg developed a serious postthrombotic syndrome (grade 3 or 4) in contrast to only 9% of those with thrombosis of the lower leg

DISCUSSION

The most serious complications of deep vein thrombosis are pulmonary embolism and the postthrombotic syndrome Due to the lack of controlled clinical trials it is still not known which treatment is most effective for deep vein thrombosis At present the therapy of choice is hospital admission heparinization so that rapid mobilization is possible and oral anticoagulants If another therapy is to be introduced it must be shown that either the frequency of pulmonary embolism or the frequency and severity of the postthrombotic syndrome are significantly reduced

Recently thrombolytic therapy has aroused new interest Many authors are more or less favorably impressed by the results obtained with streptokinase in deep vein thrombosis (6 8 11 13 14 16 17 19 22) Two studies are comparative (3 8) and only three groups carried out a controlled trial (11 16 17 19) Hess (9) and the authors of the above mentioned studies show that streptokinase does not cause a definite reduction in the frequency of pulmonary embolism It was shown phlebographically that a thrombus disappears more rapidly with streptokinase than with heparin treatment It appears that the fresher the thrombus the better the result (7 11) Although it has been reported that old thrombi react favorably to thrombolytic therapy (1 6) most authors assume that for effective thrombolytic therapy the thrombus may not be more than 5 days old

It is assumed that because streptokinase causes rapid disappearance of the thrombi the valves in the veins are preserved and therefore the postthrombotic syndrome is prevented This must still be proven clinically There have in fact been follow up studies (12 14) but as yet no good controlled clinical trial has shown clearly that streptokinase reduces the severity and frequency of the postthrombotic syndrome

In our study phlebography was not performed in the acute stage of the deep vein thrombosis because we were not interested in the direct effect of heparin and streptokinase on the thrombus A clinical differentiation was made between thrombosis of the upper and the lower leg The extent of the swelling correlates well with the location of the thrombosis (21) When edema is restricted to the lower leg the thrombotic occlusion is located in the popliteal vein or lower A thrombotic occlusion in the femoral and/or iliac vein results in edema of the entire leg Our abnormal phlebograms confirmed the conclusion of de Weese and Rogoff (21)

We did not use phlebography to establish the diagnosis of deep venous thrombosis because our

criteria were very strict and our follow up con firmed the diagnosis On the other hand our re luctance to use phlebography was also a dis advantage because only one out of every nine suspected cases of deep venous thrombosis was accepted for the trial Therefore it took us two years to find ten patients for our prospective trial

Our study shows that of the ten patients treated in the hospital two (nos 1 and 9) still had obvious edema three months later Both patients had had thrombosis of the upper leg and had received hepa rin For both patients the venous pressure meas urements and the phlebograms were highly patho- logical The four patients with thrombosis of the lower leg (two treated with streptokinase and two with heparin) were free of complaints this was in good agreement with the data obtained from pres sure measurements and phlebography The remain ing four patients with thrombosis of the upper leg (three treated with streptokinase and one with heparin) were also without complaints Venous pressure measurements and phlebography revealed no or only slight abnormalities

Clinically the five patients treated at home with only oral anticoagulants appeared to react moder ately to poorly Mobilization was slow and return to work greatly delayed For four of the five patients the results three months later were also poor—both clinically and as far as the venous pressure meas urements and phlebograms are concerned

Because of the small number of patients no defi nite conclusion is possible in this prospective study however streptokinase does appear to give the best results in the prevention of the postthrom botic syndrome but with considerably more side effects

The retrospective study showed that there are fewer symptoms of the postthrombotic syndrome after thrombosis of the lower leg than after thrombosis of the upper leg This had already been reported (23) It is therefore obvious that strepto kinase offers little advantage to a patient with thrombosis of the lower leg We believe that pa tients with thrombosis of the lower leg should not be treated with thrombolytic agents Treatment with streptokinase of a thrombotic obstruction of the proximal large veins (iliofemoral veins) prom ises much more also according to the literature (6 13) The present controlled clinical trial will be continued only with patients with thrombosis in the femoral and/or iliac veins in order to determine whether streptokinase gives significantly better re sults than heparin This will be a prolonged in vestigation because in some cases heparin appears to give excellent results

On the basis of the prospective and retrospective studies the following conclusions can be drawn (*a*) The prognosis with respect to the post thrombotic syndrome for patients with thrombosis of the lower leg is favorable even in patients treated at home with only oral anticoagulants Treatment in the hospital means that initial heparinization is possible leading to a more rapid clinical improvement with fast mobilization Streptokinase is not indicated because no important gain can be expected and because of the number and severity of the side effects (*b*) The prognosis with respect to the postthrombotic syndrome for patients with thrombosis of the upper leg treated only with coumarin drugs is poor Admission to the hospital is therefore necessary Heparinization in combination with oral anticoagulants offers in ad dition faster clinical improvement with few risks As an alternative and if the thrombus is not older than 5 days streptokinase administration must be considered to further reduce the chance of the post thrombotic syndrome Only a more extensive con trolled clinical trial will clarify the position of streptokinase in the treatment of thrombosis of the upper leg

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Streptokinase Treatment of Deep Venous Thrombosis of the Lower Extremity

Clinical Phlebographic and Plethysmographic Evaluation of Early and Late Results

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ABSTRACT The investigation comprises 19 patients with acute deep vein thrombosis of the leg treated with streptokinase The acute clinical symptoms rapidly subsided in 15 patients Phlebography, performed immediately after treatment, revealed complete thrombus regression in 7 cases, restoration of venous flow but remnants of thrombi in 4 and no effect in 7 One woman was not evaluated radiologically due to pregnancy The phlebographic restoration seemed to be correlated to the duration of the thrombotic symptoms Follow up examinations 6–50 months after the thrombotic incident demonstrated normal phlebograms in 8 patients, all of whom were also free from post thrombotic symptoms Venous occlusion plethysmography confirmed that these patients had a normal venous outflow capacity and valvular function in the relevant limbs By contrast the remaining 11 patients, with more or less extensive remnants of thrombi at the follow up phlebography were found to have plethysmographic signs of venous obstruction and sometimes also valvular insufficiency The results indicate that thrombolytic treatment is able to give a complete and lasting anatomical and functional restitution of the deep veins after an acute thrombosis in the leg, provided that treatment is induced early enough

Active treatment of acute venous thrombosis by means of surgical or fibrinolytical methods has long been discussed Great hopes were set on acute venous thrombectomy (3 6 14 15) However the good primary surgical results seldom persisted when critical follow up examinations were made (9 13) Practical streptokinase therapy was not commonly employed until it was demonstrated that a standard dosage scheme could be used with advantage (18 21 22 23) The immediate clinical results of streptokinase therapy in deep venous thrombosis were early considered to be satisfactory (7 23) as also later confirmed by phlebographic studies (1 10 18 20) As after thrombectomy initially successful thrombolysis does not eliminate the risk of later rethrombosis Little is known about the extent of such rethrombosis In four published studies (11 17 18 20) of altogether 30 patients 4 suffered from rethrombosis

The aim of this study is to further elucidate the feasibility of restoring venous function in the legs after deep venous thrombosis by means of streptokinase therapy

MATERIAL

The study comprises a selected group of 19 patients with acute deep venous thrombosis of the lower extremities treated with Kabikinas* (Kabi Stockholm Sweden) at Danderyd Hospital during 1968–72

In all 28 patients were treated but nine had to be excluded from the study for various reasons Satisfactory phlebography was not performed in two of these nine patients before treatment Three had malignant diseases and succumbed during the follow-up period Two patients had such hypersensitive reactions to the contrast medium that phlebographic reexamination could not be performed One patient had died of cardiac disease and one could not be traced The group of examined patients consisted of 11 males and eight females aged 25–67 years (mean 47)

Factors of suspected aetiological significance were operation in 4 cases venous stasis 3 pregnancy 3 oral *contraceptives* 2 *earlier thrombosis* 2 *and unknown in* 5 cases The history of the thrombosis comprised less than 3 days in six cases 3–6 days in four and more than 6 days in nine The thrombosis involved the left leg in 12 cases and the right leg in seven Thrombosis with sites proximal to

the opening of the deep femoral vein have been designated as high or ileofemoral and those distal to this as low or peripheral However all thrombi were located proximally to the popliteal vein According to this designation 11 thromboses were ileofemoral and 8 peripheral The patients were blood typed before treatment Hb platelets and the TT index were checked before and during treatment Other clotting factors were not determined routinely

Streptokinase was administered according to a standardized dosage scheme (21) with an initial dose of 600 00 IU for 30 min followed by a maintenance dose of 100 000 IU/h A treatment period of about 72 hours was the objective The treatment was continued for an additional 36–96 hours in three cases however and it had to be discontinued after 36 hours in one patient Four hours after completion of the streptokinase infusion heparin was also administered i v according to a standard scheme (12 500 10 000 10 000 and 12 500 IU respectively every 6 hours) Dicumarol therapy was initiated on the following day and when a satisfactory TT index had been obtained the treatment with heparin was terminated Corticosteroids were given orally throughout the course of streptokinase treatment 15 mg prednisolone initially followed by 10 mg every 12 hours The dicumarol treatment was continued for a variable length of time usually for 3–6 months

Follow up examinations by clinical assessment and phlebography were made after 6–50 months (mean 21) in all patients Venous occlusion plethysmography was performed after a slightly longer interval Three patients had suffered rethrombosis and two were unwilling to undergo the examination thus reducing the number of patients by this time Two additional patients had to be excluded for technical reasons due to unsatisfactory

METHODS

Phlebography X ray examinations in the form of ascending centripetal phlebography (5 19) were made in all patients prior to the streptokinase treatment In three cases the contrast medium was also injected via the femoral vein in order to visualize better the veins of the pelvis In one case a catheter was inserted in a branch of the great saphenous vein which was used for both phlebography and the infusion of streptokinase (16) The phlebograms were assessed with regard to the morphology of the veins and the presence of valves

Plethysmography Venous occlusion plethysmography was performed by means of a modified Dohn plethysmograph (4) with the air filled recording cuff around the widest part of the calf Venous occlusion was produced in the lower part of the thigh with a cuff pressure of 50 mmHg A direct writing ink jet recorder (Mingograph 81 Siemens Elema Stockholm) was used for recordings

The *venous reserve volume* was defined as the segmental calf volume increase during venous occlusion at the thigh and expressed in ml/100 ml of tissue

The *maximal venous emptying capacity* was calculated from the tangent of the fast initial slope of the calf volume curve after the release of the venous occlusion cuff and expressed in ml/100 ml of tissue/min The venous reserve volume and the venous emptying capacity were measured with the patient in the supine position and the foot elevated to the level of the heart

The *venous valvular insufficiency* of the lower limb was estimated from the calf volume increase within 10 sec after a sudden 70° head-up tilting procedure from the supine position During the tilting procedure the body was supported by the contralateral limb only (2)

The methodological errors for the venous reserve volume maximal venous emptying and calf volume increase during tilting were 9 12 and 12% respectively The plethysmographic examinations were interpreted without knowledge of the phlebographic findings

EARLY RESULTS

Clinical evaluation The symptoms of thrombosis subsided quickly during streptokinase therapy in 15 of the 19 patients The leg oedema remained in four cases

Two patients were treated during the third and sixth months of pregnancy respectively In both cases there were ileofemoral thrombi in the left leg There were no complications and both patients had normal deliveries

Complications Rise in temperature above 39°C during the course of streptokinase treatment occurred in four cases Haemorrhages occurred in three patients One woman taking insulin injections exhibited extensive subcutaneous haematomas with a drop in Hb concentration from 14 to 5 g/100 ml after two days but was still allowed to complete the treatment In a male patient who had undergone an operation for a pertrochanteric fracture of the femur heavy bleeding occurred from the area of the operation The haemorrhage occurred 18 days after the operation immediately after the start of streptokinase therapy which had to be discontinued after 36 hours A man who had received an autologous vein graft in connection with a resection of the common femoral vein suffered a total occlusion of the graft seven days after the operation Streptokinase therapy was initiated and completed despite a moderate haemorrhage in the area of the operation

Suspected allergic reactions occurred in two cases A male patient experienced abdominal pain and nausea after the initiation of treatment and a fall in BP was noted The infusion was interrupted but continued following a higher dose of cortisone A female patient suffered from vomiting and flushing which disappeared when a higher dose of

Table I *Length of thrombotic history in relation to therapeutic results (assessed phlebographically) at follow up*

Length of history prior to treatment (days)	No visible changes	Post thrombotic changes
0–2	4	2
3–6	2	2
>7	2	7

cortisone was given without terminating the treatment

Phlebography Phlebography was performed in all patients before the completion of therapy except in one pregnant woman to prevent any additional radiation exposure In three cases in whom the phlebographic examination had shown an unsatisfactory therapeutic effect therapy was continued for an additional 36–96 hours whereafter a new X ray examination was made In seven cases the phlebographic examination after the completion of streptokinase therapy showed complete regression of thrombi with intact valves in the veins Another four cases showed partial thrombolysis with restored patency but valves in the relevant venous segment could not be demonstrated Seven patients had entirely unchanged phlebograms Five of these had ileofemoral and two peripheral thrombi

FOLLOW UP EXAMINATION

Clinical evaluation At the clinical follow up examination eight of the patients were entirely asymptomatic There was slight oedema of the relevant leg in eight patients and two additional patients also complained of aching One patient had aching only Skin changes of post thrombotic type did not occur in any case

Phlebography The phlebography performed in connection with the follow up examinations showed completely normal conditions in eight patients Seven of these already had normal phlebograms on completion of streptokinase therapy One patient had not been examined at that time One of the patients in whom deep venous patency was restored with minimal residual thrombi after the treatment with streptokinase developed rethrombosis one month later in spite of adequate anticoagulation In the other patients who showed residual thrombotic elements initially but restored patency the latter was preserved Phlebographically demonstrated post thrombotic changes of varying degrees were present in the cases in whom the treatment had not led to any initial results Rethrombosis occurred in three of these patients during the period leading up to the plethysmographic examination The duration of the thrombotic symptoms prior to treatment and the phlebographic findings at follow up are shown in Table I

Plethysmography The *venous reserve volume* (Fig 1*a*) in the calf as well as the segmental calf volume were identical in both legs of the patients who had normal phlebograms at follow up On the other hand patients with post thrombotic changes had lower venous reserve volumes in the thrombosed leg than in the contralateral one with a significant difference between the both legs in paired comparisons ($p<0\ 01$) while the segmental calf volume tended to be slightly larger ($p<0\ 05$)

The *maximal venous emptying capacity* (Fig 1*b*) of the legs showed no side difference in the patients who had no phlebographic changes at follow up On the other hand in patients with residual venous changes the venous emptying rate was lower for the thrombosed leg than for the contralateral one ($p<0\ 001$)

In most cases the *increase in calf volume during 70° tilting* (Fig 1*c*) was roughly equal in both legs but two patients showed at least twice the increase in volume in the thrombosed leg compared to the normal one At the follow up examination both of these patients had a total occlusion of the superficial femoral vein with marked dilatation of the great saphenous vein and venous collaterals in the thigh

DISCUSSION

Many patients in this series sought consultation concerning their thrombotic symptoms at a remarkably late stage Our results constitute further confirmation of the earlier clinical experience that this form of treatment is seldom rewarding if the thrombosis is more than six days old (Table I) The reason why the therapeutic results were not very satisfactory in two cases with short histories may be due to the possibility that there had already been non-occluding and thus clinically silent thrombi for a more or less lengthy period Thus in connection with venous thrombectomy it has been possible to demonstrate murally adherent and organized

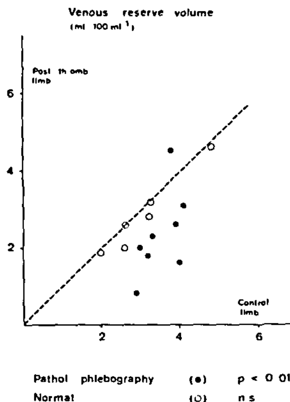


Fig 1a

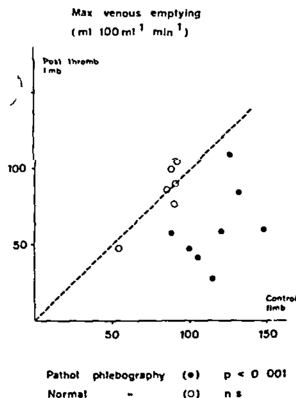


Fig 1b

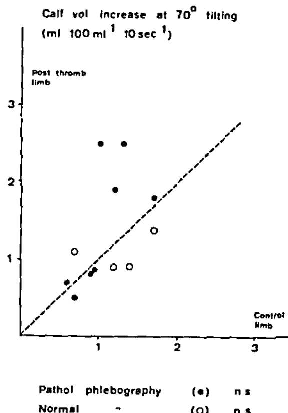


Fig 1c

Fig 1 (a b c) Plethysmographic variables obtained at the follow-up examination of the post thrombotic limb as compared with corresponding observations on the contra lateral limb --- = lines of identity the *p*-values give the significance of the differences at paired comparisons within the respective patient groups

thrombi in patients with histories of clinical thrombosis of less than two days (9)

The literature shows variable data on the results of thrombolytic therapy in acute venous thrombosis perhaps due to differences in patient selection and radiological evaluation Because of the inherent difficulty in rating phlebographic findings we have limited our assessment to the question of whether the thrombosed veins were entirely free from thrombotic remnants or not while the venous flow capacity and valvular function were evaluated plethysmographically The present observation of full radiological restoration in 8 of 19 cases is in good agreement with earlier studies having an average success rate of 35% (1 12 17 18 20)

Side effects in connection with streptokinase therapy are still a problem Even if conventionally

accepted contraindications are observed haemorrhagic complications are noted on an average in 35% temperature rise in 40% and allergic reactions in 10% of the patients (8) In only one case it was necessary to discontinue the treatment earlier than planned because of side effects It should be observed that it was possible to carry out thrombolytic therapy even during the course of pregnancy

The phlebograms of the patients showing good primary results were still normal at the follow up 6–50 months later These patients were completely asymptomatic and the plethysmographic examination confirmed normal venous function in the leg in question On the other hand post thrombotic symptoms and increased calf volume were frequently observed in the patients whose follow up phlebograms showed more or less extensive remnants of thrombi In addition the plethysmographic control of these patients showed a smaller venous reserve volume and a reduced venous *emptying rate The decrease in the venous reserve* volume is probably connected with the extent of venous thrombosis while the lower emptying rate reflects a decrease in the venous outflow capacity The good correlation with phlebography in these cases corroborates the validity of the plethysmographic assessment

The purpose of the studies on changes in calf volume during tilting was to estimate venous valve insufficiency Using the same method Bygdeman et al (2) have shown that the calf volume increases pathologically in cases in whom a reflux of the contrast medium from the groin down to the thigh or possibly the calf can be demonstrated by retrograde phlebography The asymmetrical increase in calf volume during tilting found in two cases in this follow-up is *probably a manifestation of functional* valvular insufficiency in the dilated collaterals bridging the still occluded deep venous trunk in the thigh The normal valvular function in patients without thrombotic remnants at phlebography contrasts with the valvular destruction observed after venous thrombectomies (13) and constitutes an important argument in favour of thrombolytic therapy in acute venous thrombosis

CONCLUSIONS

1) Streptokinase treatment of acute venous thrombosis in the leg resulted in initial complete thrombolysis as evaluated by phlebography in 8 of 19 patients (40%) 2) The therapeutic failures could be attributed to a late consultation in the course of the disease with few treatments being successful if induced after a clinical history of more than 6 days 3) The complications of the thrombolytic therapy were moderate and usually managed without interrupting the treatment 4) The follow up investigation 6–50 months after the thrombolytic therapy based on phlebography and venous occlusion plethysmography indicates that an initial complete thrombolysis insures a good chance of obtaining a lasting restoration of deep venous anatomy and function without post thrombotic symptoms and signs of venous obstruction or valvular insufficiency 5) The follow up study demonstrates a good correlation between phlebography and venous occlusion plethysmography in the assessment of post thrombotic venous obstructions

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The information in the literature regarding the connection between administration of corticoid hormones coagulation and thromboembolism is scanty and inconsistent Increased coagulability in connection with the administration of corticoids and of ACTH to man was reported by Cosgriff et al (8) Cosgriff (7) and Chatterjea and Salomon (5) Ozsoylu et al (26) demonstrated shortening of coagulation time and an apparent increase in the level of factor VIII in one patient with Cushing s syndrome Of interest in this connection is also the recent finding by Isacson (16) of a hypofibrinolytic condition and decreased plasminogen activator in the walls of superficial veins of prednisone treated healthy subjects

On the other hand no increased frequency of thromboembolic complications or obvious coagulation disorders after corticoids or ACTH were reported by other authors (13 30 31) In a discussion on the relation between corticosteroids and thrombosis Cope (6) concluded that the question must be considered unsettled

The present paper strongly supports the idea of a relationship between overproduction of cortisol in Cushing s disease elevation of factor VIII in the blood and the increased incidence of thromboembolism in this disease

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Leucocyte Migration Inhibitory Activity of Concanavalin-A-stimulated Human Lymphocytes

Modification by Dipyridamole Lysine-acetylsalicylate and Heparin

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ABSTRACT The in vitro effects of heparin, dipyridamole (DIPY) and lysine-acetylsalicylate (LASA) on human peripheral blood leucocyte migration and upon production/release and effect of leucocyte migration inhibitory activity (LMIA) from lymphocytes stimulated with concanavalin A (con A) have been studied The final concentration of each drug was of the same order of magnitude as during clinical treatment. The leucocyte migration under agarose was significantly increased by DIPY at a concentration of 100 μg/ml The release/production of LMIA was inhibited by DIPY at 1 μg/ml and by LASA at 0 3 μg/ml Heparin had no influence on LMIA release, even at 10 IU/ml The LMIA of supernatants from con A stimulated lymphocyte cultures was inhibited by DIPY at a concentration of 10 μg/ml, by LASA at 3 μg/ml and by heparin at 10 IU/ml The findings suggest that DIPY and LASA could have a dual role as modifiers of inflammation 1) the well known role as antiaggregants tending to limit and impede thrombosis and 2) as antagonists to the lymphocyte-mediated (type IV) immune reaction through a depressive action on lymphokine production/release and activity

The evident role of thrombosis and extravascular fibrin deposits in immunoinflammatory reactions (14) has initiated attempts to use anticoagulants (e g heparin dicumarol) antiaggregants (e g dipyridamole acetylsalicylic acid lysine acetylsalicylate) or combinations of such drugs for the treatment of clinical disorders with immunoinflammatory tissue damage A beneficial effect of this therapy in combination with other types of medical treatment is reported in kidney-allografted patients (21 24) heart allografted patients (18) systemic lupus (28 29) rapidly progressing glomerulonephritis (8) proliferative glomerulonephritis (11 22 33) and thrombotic microangiopathy (1) It is not clear however whether the apparent effect is obtained as assumed mainly or exclusively through drug induced antagonism of the coagulation system since some drugs with such activity possess other effects that can modify the immune response and the inflammatory process (4 9 10 11 15 17 26)

Lymphokines are lymphocyte released factors which act as non specific mediators of inflammatory damage in cell mediated (type IV) immune reactions They are released from T effector lymphocytes upon specific reaction with antigen or from T and B lymphocytes stimulated by mitogens for instance concanavalin A (con A)

The present study examines whether some drugs with anti thrombotic activity (dipyridamole (DIPY) lysine acetylsalicylate (LASA) and heparin in clinically relevant concentrations (13) can 1) modify the in vitro migration of human peripheral blood leucocytes 2) modify the con A induced lymphocyte production/release of leucocyte migration inhibitory activity (LMIA) and 3) modify the in vitro effect of LMIA on migrating peripheral blood leucocytes

MATERIAL AND METHODS

Drugs

DIPY (Persantin® Boehringer Ingelheim Germany) LASA (Aspégic® Egic Montargis France) and heparin (Leo Ballerup Denmark) were diluted/dissolved in tissue

Table I *The final concentrations of heparin dipyridamole and lysine-acetylsalicylate used in the experiments compared with the clinically relevant plasma concentrations of the respective drugs*

	Concentrations used in the experiments	Therapeutic plasma concentration
Heparin (IU/ml)	0 1	
	1	1–4
	10	
DIPY (µg/ml)	1	
	10	1–10
	100	
LASA (µg/ml)	0 3	
	3	200–300
	30	

culture medium 199 with penicillin 67 IU/ml and streptomycin 67 µg/ml (Difco Laboratories Michigan USA) (TC 199) *The concentrations employed were comparable to clinically relevant plasma concentrations* as shown in Table I 0 9 g LASA is equivalent to 0 5 g acetylsalicylic acid (ASA) All preparations of drugs were stored at −20°C until use

LMIA production/release

LMIA was obtained as previously described by Bendtzen et al (6) A 95–99% pure mononuclear cell population was obtained from venous blood of healthy male and female human adults by centrifugation in Ficoll isopaque (Lym ... Nyegård Oslo Norway) Con A 250 µg (Phar... Uppsala Sweden) in 50 µl TC 199 was added ... 5×10⁶ cells suspended in 3 ml TC 199 and incubated ... 22 hours at 37°C in water saturated air with 2% CO_2 After centrifugation for 10 min at 670 *g* all biologically active con A was removed from the supernatants by passage through a Sephadex G 100 column (Pharmacia Uppsala Sweden) (6) 9 ml eluate was collected and tested for LMIA An identical 3 ml con A free mononuclear cell suspension was treated in parallel the supernatant being reconstituted with 250 µg con A immediately before passage through the Sephadex column

LMIA assay

LMIA was measured with a modified indirect leucocyte migration agarose technique (ILMAT) as previously described by Clausen (12) and Bendtzen et al (6) The migrating indicator cell population consisted of peripheral blood leucocytes from unrelated healthy human adults The LMIA was expressed as a migration index (MI) in the following way

$$MI = \frac{\text{mean migration area with con A stimulated culture supernatant}}{\text{mean migration area with control culture supernatant}}$$

Assay for direct drug effect on leucocyte migration

Before migration 22×10^6 leucocytes were suspended in 90 µl TC 199 (control) and in 90 µl TC 199 containing different concentrations of the drug After incubation at 37°C for 90 min the migration capacity was measured by the ILMAT (24 hours) and the effect of the drug on the migration (MI_{drug}) was expressed in the following way

$$MI_{drug} = \frac{\text{mean migration area of drug treated leucocytes}}{\text{mean migration area of control leucocytes}}$$

Assay for drug effect on LMIA production/release

The ILMAT as described above was used and the drugs tested were included both in the con A stimulated 3 ml cell suspension and in the non stimulated control cell suspension during the entire incubation period The con A preincubated and the con A reconstituted supernatants were subsequently passed through Sephadex G 100 columns and examined for LMIA The calibration of the columns allowed only molecules larger than 10000 daltons to be eluted thereby retaining DIPY and LASA but not heparin (17000 daltons) (5)

The influence of a drug on LMIA production/release was calculated by comparing the MI under influence of the drug during incubation in the con A stimulation period (MI (LMIA production)$_{drug}$) with the MI in the parallel control without drug influence (MI (LMIA production)$_{control}$) according to the following formula

$$\%\ \text{inhibition} = \frac{\text{MI (LMIA production)}_{drug} - \text{MI (LMIA production)}_{control}}{1 - \text{MI (LMIA production)}_{control}} \times 100$$

Assay for drug influence on LMIA effect

After LMIA production/release as described above and elution on Sephadex G 100 the drugs were added to both the con A preincubated lymphocyte supernatants and the con A reconstituted control supernatants so as to form the final concentrations indicated in Table I

The LMIA in the mixtures was subsequently measured using the ILMAT The influence of a drug on the LMIA effect was calculated by comparing the MI in presence of the drug (MI (LMIA effect)$_{drug}$) with the MI in absence of the drug (MI (LMIA effect)$_{control}$) according to the following formula

$$\%\ \text{inhibition} = \frac{\text{MI (LMIA effect)}_{drug} - \text{MI (LMIA effect)}_{control}}{1 - \text{MI (LMIA effect)}_{control}} \times 100$$

Calculations

Each experiment was set up in quadruplicate and all reported values again represent means of parallel experiments with four different cell populations Student's *t* test for paired data was used for the calculation of significant differences

Table II *Direct effect of heparin dipyridamole and lysine acetylsalicylate on leucocyte migration*

	Concentration	MI_{drug} ±S E M	p
Heparin (IU/ml)	0 1	1 ±0 05	n s
	1	0 93±0 06	n s
	10	0 83±0 06	n s
DIPY (μg/ml)	1	1 15±0 05	n s
	10	1 35±0 14	n s
	100	1 44±0 13	<0 05
LASA (μg/ml)	0 3	1 25±0 08	n s
	3	1 09±0 10	n s
	30	0 90±0 03	n s

p>0 05 was considered not significant n s =not significant

RESULTS

Direct drug effect on leucocyte migration
(Table II)

In the concentrations used heparin did not show any significant influence on the leucocyte migration At increasing concentrations there is a gradual decrease of the MI_{drug} but the differences which may indicate a toxic" heparin effect are insignificant DIPY tends to increase the MI_{drug} the highest concentration employed causing significant stimulation at the 5% level LASA seems to stimulate the MI_{drug} in low concentrations but the differences are insignificant

Effect of drugs on LMIA production/release
(Tables III and IV)

Since heparin was not removed by passage through Sephadex G 100 an effect during the second step of the ILMAT may have influenced the results However a modifying effect on LMIA action could be detected only at the highest concentration of heparin as shown in Table IV As to the other drugs examined DIPY and LASA were highly active as inhibitors of LMIA production at all concentrations used (Table III)

Modification by drugs of LMIA effect

Heparin does not cause any significant inhibition of the LMIA effect in the two lowest concentrations employed In the highest concentration the LMIA effect is antagonized with a probability at the 5% level DIPY and LASA caused significant inhibition of the LMIA activity at the middle and highest concentrations used (Table IV)

DISCUSSION

The con A triggered production/release of LMIA from peripheral blood mononuclear cells utilizes the ability of con A to simulate the specific reaction between antigen and antigen-directed lymphocyte membrane receptor presumably mainly with T but also with B lymphocytes (6) Con A stimulation is known to lead to in vitro events that are typical of the specific in vitro response of lymphocytes to antigen and this includes the induction of lymphokine production/release The observations in the present study are therefore not automatically valid for events following specific antigen lymphocyte reactions but as in other in vitro experiment with mitogens comparison and analogy suggest a high degree of resemblance The examination of LMIA

Table III *Drug influence on LMIA production/release*

	Concentration	MI (LMIA production)$_{control}$ (mean of MI)	MI (LMIA production)$_{drug}$ (mean of MI)	Inhibition of LMIA production (%)	p
Heparin (IU/ml)	0 1		0 81±0 04	40 6	n s
	1	0 68±0 06	0 83±0 02	46 8	n s
	10		0 82+0 04	43 7	n s
DIPY (μg/ml)	1		0 79±0 02	47 5	<0 05
	10	0 60±0 05	1 03+0 03	100	<0 01
	100		1 03±0 02	100	<0 01
LASA (μg/ml)	0 3		0 86+0 05	53 3	<0 025
	3	0 70±0 02	1 05±0 03	100	<0 01
	30		0 95±0 02	83 3	<0 01

Statistical symbols as in Table II

Table IV *Drug influence on LMIA effect*

	Concentration	MI (LMIA effect)$_{trol}$ (mean of MI)	MI (LMIA effect)$_{drug}$ (mean of MI)	Inhibition of LMIA effect (%)	p
Heparin (IU/ml)	0 1		0 68±0 06	31 9	n s
	1	0 53±0 06	0 67±0 06	29 7	n s
	10		0 72±0 04	40 4	<0 025
DIPY (µg/ml)	1		0 67±0 05	31 2	n s
	10	0 52±0 03	0 88±0 03	75 0	<0 01
	100		0 94±0 01	87 5	<0 01
LASA (µg/ml)	0 3		0 83±0 06	46 8	n s
	3	0 68±0 04	0 93±0 01	78 1	<0 01
	30		0 99±0 01	96 8	<0 01

Statistical symbols as in Table II

production/release and LMIA effect and the modification of these processes by certain chemicals in the present system is restricted by these considerations

In order to obtain conclusive information on the LMIA release/production and LMIA effect and to assess the in vitro modification of these processes by chemicals at different concentrations it was a clear advantage however to work in an antigen free system Thereby it was possible in the two-step technique to exclude sources of error such as non specific LMIA releasing capacity of antigen in mplete removal of antigen from first to second of the ILMAT and unforeseen specific tigen-dependent reactivity of a presumed unrelated indicator cell population Another advantage of the con A release/production system is a considerably higher yield of LMIA than with antigen stimulation of a specifically reactive lymphocyte population This makes it possible to obtain more clear observations of the LMIA effect and its antagonists The ILMAT for measuring con A released/produced LMIA utilizes and depends upon the fact that it is possible to remove all biologically active con A (6) from the stimulated lymphocyte supernatants between the first and second steps of the ILMAT

Heparin effects

Heparin is a physiological anticoagulant of blood Biologically highly active in several other respects as for instance in lipid metabolism (lipodispersant action) (31) and water saline metabolism (33) the great therapeutical potential of heparin is increased by its anti inflammatory action (decrease of capillary permeability inhibition of histamine and plasmakinin effects anticomplementary action inhibition of hyaluronidase) (30 31 32 33)

The anticoagulant and the anti inflammatory effect has inspired attempts to use heparin for the prevention and treatment of the Shwartzman phenomenon (30) and several other types of non immunological inflammation in animal experiments and in clinical work (19 31) Encouraging reports on the use of heparin in the prevention and treatment of thrombotic processes associated with immunological diseases have appeared recently (3 28 29 33)

In view of the broad spectrum of activities influenced by heparin and since heparin is commonly used in clinical therapy to influence thrombotic and inflammatory damage we decided to examine the influence of heparin on leucocyte migration which is one important functional entity of the inflammatory process As a starting point one might expect heparin in some way to modify the migratory capacity of leucocytes since heparin is a highly electronegative compound which could change cell membrane properties through interference with the cell membrane potential The same interference might cause modification of lymphokine production/release and lymphokine activity With the experimental system used however an expected change in the form of migration inhibition is induced only by high clinically non relevant concentrations of heparin and the observation does not support theories of an anti inflammatory effect of heparin at the leucocyte lymphocyte level

DIPY and LASA effects

DIPY was used previously as a vasodilator agent and was later discovered to inhibit thrombocyte aggregation by inhibition of the breakdown of adenosine in plasma (17) DIPY antagonizes the thrombocyte aggregating effect of adenosine diphosphate (ADP) epinephrine thrombin and collagen all substances that cause a decrease of the cell contents of cyclic adenosine monophosphate (cyclic AMP) (4 17 25)

Previous studies have shown that an increase of cyclic AMP in lymphocytes prevents lymphokine production/release (23 27) A similar effect applies to thrombocytes substances such as theophylline which increase the cyclic AMP content in thrombocytes (4) inhibit the thrombocyte aggregant release and substances which decrease the cyclic AMP level in thrombocytes enhance the thrombocyte aggregant release and thereby thrombocyte aggregation (4) Such proaggregant substances are known to participate at least in one type of leucocyte activation increase of leucocyte adhesivity (11)

All these observations and considerations tend to suggest a similar basic mode of action of some drugs on thrombocytes and leucocytes ASA and its soluble and injectable derivative (LASA) (2) are known for their anti inflammatory activity They increase lysosome stability (10) decrease production and activity of vasoactive amines (4) inhibit leucocyte adhesivity phagocytosis (9) and possibly migration (15) decrease capillary permeability and decrease production and activity of prostaglandins (4 16 17 28) ASA seems to depress the phytohaemagglutinin induced blast transformation of lymphocytes (26) and ASA and LASA have a depressive effect on thrombocyte aggregation induced by thrombin collagen catecholamines or ADP (17)

Against this background one might expect DIPY and LASA to inhibit lymphokine production and activity and in the present experimental system this was confirmed It was shown that inhibition of lymphokine production/release and activity occurred at clinically relevant concentrations of the two compounds The effect was obtained with concentrations of LASA 100 times lower than the maximal levels reached during clinical treatment Experiments with ASA gave comparable results

In all concentrations used DIPY seemed to increase the leucocyte migration A similar effect is probably exerted by LASA at low concentrations but this was not significant in the present study The effect may be associated with the ability of DIPY to preserve the amount of ADP–ATP in cells increasing their survival time (34) but is insufficiently explained

CONCLUSION

The in vitro system employed in this study has not exposed any leucocyte or lymphocyte dependant anti inflammatory properties of heparin in relevant concentrations As to DIPY and LASA the system has revealed modifying effects on leucocytes and on lymphocyte functions associated with inflammation If the findings are hypothetically extended to in vivo conditions they suggest that the two compounds can inhibit certain lymphokine activities possibly even lymphokine production/release This assumption would give DIPY and LASA a dual role as modifiers of inflammation 1) a rather well established role as antiaggregant compounds tending to limit and impede thrombosis and 2) a role as antagonists to the lymphocyte mediated type IV immune reaction through inhibition of lymphokine production/release and activity

An important step towards substantiating this theory will be a repetition of the present experiments using an antigen-dependant LMIA release system and a comparison of con A released and antigen released LMIA as to biological as well as biochemical identity Another approach for assessing the relevance of the in vitro findings in relation to in vivo conditions is possible through quantitative examinations of con-A releasable LMIA in patients before and during treatment with adequate doses of DIPY and LASA Such studies are presently in progress in our department

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Sequential Studies of Lymphocytes, Neutrophils and Serum Proteins during Prednisone Treatment

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ABSTRACT Seven patients (6 with connective tissue diseases, 1 with bronchial asthma) have been studied before, during and after prednisone therapy Maximum dose was 15 mg daily, which was tapered off to zero within three months All patients showed striking subjective improvement during therapy The ESR reflected this improvement but the acute phase proteins did not The serum concentration of prealbumin rose significantly during the period of most intensive steroid treatment IgE decreased in the patient with bronchial asthma but otherwise the immunoglobulins did not change, and positive serological tests remained unchanged Contact sensitization to haptens was induced without impairment during therapy Prednisone induced rises in blood lymphocyte and neutrophil concentrations Lymphocyte transformation both mitogen and antigen induced was not influenced by therapy but PPD induced inhibition of leucocyte migration decreased Neutrophil phagocytosis was unimpaired, but bactericidal capacity, stimulated nitroblue tetrazolium reduction, and neutrophil and plasma lysozyme concentrations were all depressed during treatment with prednisone

The mechanisms behind the immunosuppressive and anti inflammatory effects of glucocorticosteroids are not well understood Steroids modify many reactions within the various parts of the immune system but the relative importance of these modifications for the clinical effect observed is not known (6) In particular moderate and minor dosages of steroids are often effective in controlling the clinical manifestations of immune and allergic disorders but studies to elucidate the function of various components of the immune system in patients during such treatment are scarce

This paper describes sequential laboratory investigations in seven patients who were treated with prednisone The initial dose was 15 mg daily which was later tapered off again to zero during the period of study The parameters studied included functions of lymphocytes and neutrophils and concentrations of plasma proteins of the inflammatory and immune response

MATERIAL AND METHODS

Patients from our Follow-up Clinic of Immunologic Disorders were selected according to the following criteria 1) no previous treatment with steroids 2) insufficient effect of conventional non steroid treatment 3) disease manifestations of such limited severity that a dose of 15 mg prednisone *daily* was *judged to be sufficient for control of* symptoms

Seven consecutive out patients fulfilling these criteria were followed Their diagnoses and other pertinent clinical data are given in Table I In all patients the serum creatinine concentration was within normal limits and no infectious episodes occurred during the period of observation The purpose and the plan of the study were explained to the patients and their consent was obtained The treatment schedule was starting dose 15 mg prednisone per day (5 mg three times daily) which was continued for 1 month over the following 2 months the dose was tapered off to zero Antacid was given routinely during the period of prednisone treatment

The patients were studied twice before the start of prednisone treatment once a month during treatment and one month if possible also two months after cessation of *treatment At each visit the clinical status was ascer*

Table I *Clinical data of the patients studied*

Pat no	Sex	Age (y)	Diagnosis	Duration of disease (y)	Non steroid treatment Before therapy	During therapy
1	♀	71	Systemic lupus erythematosus	6	–	–
2	♀	56	Unclassified connective tissue disease	1	–	–
3	♂	64	Bronchial asthma	1/2	–	–
4	♀	71	Polymyalgia rheumatica	1/2	–	–
5	♀	63	Systemic lupus erythematosus	12	Phenylbutazone 200 mg daily	Phenylbutazone 200 mg daily
6	♀	38	Rheumatoid arthritis	1/4	Phenylbutazone 300 mg daily for 1/4 y	–
7	♀	53	Dermatomyositis	1	–	–

tained and blood was drawn for analyses of lymphocyte neutrophil Hb and eosinophil concentrations and ESR according to Westergren All determinations were made by standard laboratory methods

Serum concentrations of prealbumin albumin α_1 antitrypsin orosomucoid haptoglobin IgG IgA and IgM were quantitated by rocket immunoelectrophoresis (18) Antisera from rabbits were obtained from Dako Copenhagen The serum samples were stored at −20°C for less than 9 months and were all examined simultaneously The determinations were made in duplicate (coefficient of variation <5%) and the results were expressed in g/l by comparison with a standard serum from Behringwerke Lahn West Germany A 95% range for the individual proteins based upon 150 normal persons 19–93 years of age has been published previously (17)

The concentration of IgE was determined by radio immunosorbent technique (Phadebas Pharmacia Uppsa ...den) The concentrations were expressed in U/ml ...son with a WHO standard (1 U≈2 4 ng) The ...ent of variation between duplicate determinations ... 10% The normal range was calculated as 95% range in 250 blood donors (Weeke unpublished)

Lymphocyte transformation was studied following stimulation by mitogens (phytohaemagglutinin (PHA) concanavalin A (con A) and pokeweed mitogen (PWM)) and by microbial antigens (PPD and an extract of Candida albicans) (2)

The leucocyte migration test (LMT) was performed according to the agarose technique described by Clausen (7) PPD was used as antigen at a concentration of 100 μg/ml The migration inhibition induced by PPD was expressed as a migration index (MI) which is the ratio between the average areas of PPD containing cultures and of cultures without PPD

Neutrophil function A) Ingestion and intracellular killing of Staphylococcus aureus were measured in a fluid phase reaction system in the presence of 10% pooled human serum (12) Ingestion is recorded as viable intra cellular bacteria in cells treated with 10 mM sodium azide (NaN_3) which blocks killing and killing is recorded as the difference in viable intracellular bacteria between NaN_3 treated and untreated cells Results were calculated as the ratio patient/normal control B) Unstimulated and stimulated nitroblue tetrazolium (NBT) tests were carried out as described previously using culture filtrates from Klebsiella pneumoniae and from Enterobacter species as stimulants (11) Results were calculated as the ratio of NBT positive neutrophils in stimulated tests over un stimulated tests

The activity of the bacteriolytic enzyme lysozyme was measured in neutrophils and in plasma (with EDTA as anticoagulant) by the turbidometric method of Litwack (13) with human lysozyme as standard (provided by Professor E F Osserman Columbia University New York) as previously described (9)

The blood volume drawn once a month for these studies amounted to 120 ml The patients were given an oral supplement of iron during the study period

In each patient the results obtained in a given test before treatment were averaged and this figure was assigned the value of 100% The following monthly observations were calculated in relation to this initial value The points given in the graphs are the averages of the individual relative values For statistical evaluation the method of paired comparison was employed relating each monthly result to the initial value

Contact sensitization was attempted by the epicutaneous application of 1000 μg dinitrochlorobenzene (DNCB) and 2000 μg p nitrosodimethylaniline (NDMA) dissolved in 100 μl acetone and applied on the volar surface of the forearm The test was read on day 13 a challenge dose of 1/10 of the sensitizing dose was applied on day 13 and read on day 16 One hapten was applied before the start of prednisone treatment the other after 8 weeks treatment The sequence of the haptens was alternated between patients

RESULTS

The scheduled treatment was followed without modifications and no side-effects were observed

All patients showed a striking clinical improvement and recovered from general malaise The body temperature was normalized in 3/3 joint pains improved or disappeared in 4/4 muscular pains im

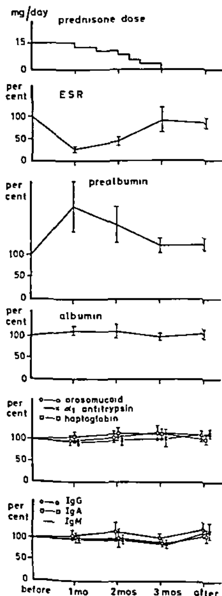


Fig 1 ESR and concentrations of eight serum proteins before during and after prednisone treatment Averages of the relative values are given 100% being defined as initial value in each patient Vertical bars = ±S E M

proved in 1/1 SLE cutaneous elements disappeared in 1/1 salivation reappeared in 1/1 and asthmatic dyspnea decreased in 1/1

Shortly after discontinuation of prednisone exacerbations occurred necessitating treatment with prednisone in three and with chloroquine in two patients

Figs 1–4 present the sequential fluctuations of the parameters studied

ESR was elevated initially in all patients but one (no 3) the pathological values ranging from 27 to 68 mm After the first month of treatment the ESR was normalized in all patients (Fig 1) this decrease being statistically significant ($p<0\ 05$) The gradual tapering off of prednisone was accompanied by rises in the ESR to almost initial values

The average initial serum concentration of prealbumin was 0 19 g/l which is within the normal range of 0 12–0 39 g/l (±2 S D) During the period of most intensive prednisone treatment the concentration rose in all patients (Fig 1) to an average value of 0 29 g/l this increase is statistically significant ($p<0\ 01$) During the tapering off of prednisone treatment the prealbumin concentration again decreased to initial values

The concentration of serum albumin (Fig 1) showed no significant fluctuations during the period of study establishing a baseline for the changes observed in the concentrations of other serum proteins The average initial value of 35 5 g/l is just below the lower limit of the normal range (37 6–54 9 g/l)

The acute phase reactants showed the following average initial concentrations (normal ranges within parentheses) orosomucoid 1 22 g/l (0 48–1 26) α_1 antitrypsin 2 03 g/l (0 98–2 45) and haptoglobin 4 14 g/l (0 58–3 73) The observed initial values were above the upper normal limit in 3/7 1/7 and 4/7 respectively As opposed to the ESR no significant changes were observed in the acute phase reactants during prednisone treatment (Fig 1)

The average concentrations of IgG IgA and IgM were within the normal range with values of 13 3 1 80 and 0 92 g/l respectively individual values were elevated in 2/7 0/7 and 1/7 No significant changes were observed during the treatment period (Fig 1)

Positive serological tests (ANF LE cells RAT irregular WR) remained unchanged

The blood lymphocyte concentration was initially within the normal limits in all patients with an average value of $1\ 9\times10^9$/l A statistically significant rise ($p<0\ 05$) was observed during treatment (Fig 2) the concentration returning to normal values during the tapering off of prednisone

The ^{14}C thymidine incorporation of unstimulated lymphocytes (Fig 2) showed no significant changes during the period of prednisone treatment but val

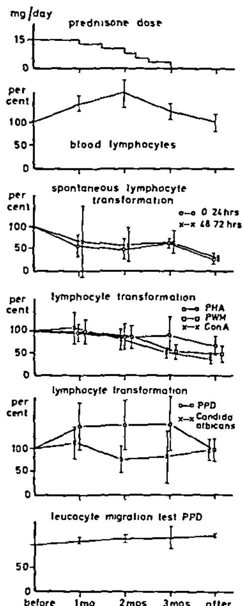


Fig 2 Blood lymphocyte concentration spontaneous lymphocyte transformation in vitro mitogen and antigen induced lymphocyte transformation and results of the leucocyte migration test in the presence of PPD Averages of the relative values are given 100% being defined as initial value in each patient Vertical bars = ±S E M

ues after cessation of treatment were lower than the initial values The same holds true for mitogen stimulation the average pretreatment values were for PHA 12 200 c p m for con A 7 000 c p m and for PWM 4 100 c p m all of which are within the normal limits of our laboratory Antigen stimulation of lymphocytes in vitro was done with PPD and with an extract of Candida albicans 2/7 showed no response to these antigens The c p m of the responders showed no significant changes during prednisone treatment (Fig 2)

All patients showed evidence of previous sensitization to PPD as judged by inhibition of leucocyte migration in vitro pretreatment MI was less than 0 79 in all patients and averaged 0 62 During treatment all patients showed decreasing PPD

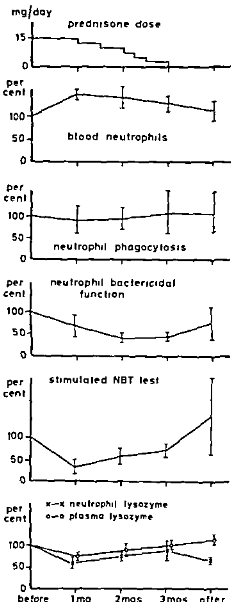


Fig 3 Blood neutrophil concentration three parameters of neutrophil function and concentrations of lysozyme within neutrophils and in plasma Averages of the relative values are given 100% being defined as initial value in each patient Vertical bars = ±S E M

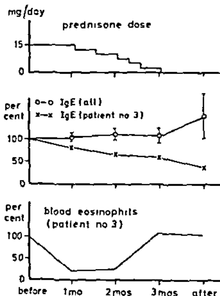


Fig 4 Serum IgE concentration in all patients and in patient 3 (bronchial asthma) together with blood eosinophil concentration in patient 3 The values given are relative to the initial value = 100% Vertical bars = ±S E M

induced migration inhibition as evidenced by rises in MI to an average value of 0 82 four showed no significant inhibition (MI above 0 79) after treatment However by the statistical method employed this rise is not significant

The concentration of neutrophils in the blood (Fig 3) showed a statistically significant rise ($p<0\ 05$) during prednisone treatment with a gradual decrease when prednisone was tapered off The average values observed were within normal limits throughout the study

The ingestion of Staphylococcus aureus by neutrophils in vitro was normal at the outset and remained so But a statistically significant decrease ($p<0\ 02$) in bactericidal capacity occurred the average initial ratio was 0 91 and the nadir was observed after two months treatment

Spontaneous NBT reduction (unstimulated tests) was normal in all patients throughout the study and did not decrease during treatment Stimulated NBT tests showed an average initial ratio of 11 0 which is normal but were markedly decreased after 1 month s treatment ($p<0\ 05$) thereafter returning to normal values

The concentrations of lysozyme in neutrophilic granulocytes and in plasma were normal at the outset and averaged 2 5 μg/10^6 neutrophils and 4 0 μg/ml plasma They decreased in parallel during the period of most intensive prednisone treatment but only the fall in plasma lysozyme reached statistical significance ($p<0\ 05$) Both again increased when prednisone was tapered off

The serum concentration of IgE remained constant throughout the study except in the patient with bronchial asthma (Fig 4) his initial values were 170 U/ml (normal range 20–650) and decreased considerably during prednisone treatment His blood concentration of eosinophils was depressed during the two months of most intensive prednisone treatment (Fig 4)

It was possible to induce contact hypersensitivity to a hapten DNCB or NDMA in 6/7 patients and the ability to be sensitized was preserved during treatment The intensity of the cutaneous inflammatory response was unchanged during prednisone therapy

DISCUSSION

The advantage of sequential studies was apparent in this study Even with a small number of patients it was possible to demonstrate significant changes during treatment with prednisone in moderate doses This was possible even when the prednisone induced changes were within the so-called normal ranges which in most instances are very wide due to interindividual variation It must of course be realized that when a large number of parameters are studied significant changes may occur by chance alone However the results obtained fit in with and extend what is known from previous studies

The effects of moderate prednisone doses are well known in clinical work However in most clinical studies of relevant laboratory parameters high doses of steroids have been employed In this study the maximum prednisone dose was 15 mg daily equivalent to 2–3 times the normal glucocorticosteroid production in man

The patients studied were females with connective tissue diseases and one male with bronchial asthma Their disease manifestations were sufficiently pronounced to motivate steroid treatment in all cases the clinical symptoms were satisfactorily controlled by the dosages employed Following cessation of treatment recurrence of symptoms was seen in all patients

Among the indicators of inflammation employed

in this study the ESR showed complete normaliza tion during prednisone treatment In contrast to this the acute phase proteins did not decrease significantly Thus the ESR paralleled the clinical course whereas the acute phase proteins may have reflected underlying disease processes not influ enced by treatment with steroids in this moderate dosage Somewhat differently McConkey et al (15) found that patients with rheumatoid arthritis receiving 7 5–10 mg prednisone daily showed a de crease after 2–6 weeks of treatment not only in ESR but also in serum haptoglobin concentration how ever the effect on haptoglobin was less than that on ESR

The concentrations of IgG IgA and IgM re mained stable as did the positive serological tests with large short term steroid doses serum IgG con centrations decrease in normal adults due to in creased catabolism and decreased synthesis (4)

The concentration of prealbumin rose during prednisone treatment This was also demonstrated in uraemic patients receiving steroids (19) and may reflect a carrier function of this protein for steroid hormones

In man as opposed to several animal species lymphocytopenia is usually not observed during steroid treatment (6) the present study even dem onstrated a moderate increase in blood lymphocyte concentration The decrease in PPD induced leuco cyte migration inhibition observed during and after atment may mean that some memory cell func is abolished by prednisone but other explana s are equally possible More studies are needed to confirm this finding and to examine the effects of steroids in this test system on lymphocytes and phagocytes separately Lymphocyte transformation was unimpaired during steroid treatment the de crease after cessation of treatment may reflect the clinical deterioration of the patients (2)

Neutrophil leucocytosis during steroid treatment is due to a prolonged transit time in the blood and not to changes in production rate (3) This is con firmed by the present observation that the plasma lysozyme concentration which is believed to re flect neutrophil turnover (8) bore a constant rela tionship to intraneutrophil lysozyme concentra tion (Fig 3) The latter however was depressed during steroid treatment which is in accordance with the observation of decreased neutrophil lyso zyme concentration during the stress of infection (10)

Decreased stimulated NBT reduction in patients receiving steroids has been noted previously (5 16) and the present studies add to this information by indicating a dose dependent relationship (Fig 3) Steroid treatment also caused a significant decrease in neutrophil bactericidal capacity (Fig 3) a func tional defect not established previously in humans This defect can be located to malfunction of myelo peroxidase mediated systems which depend upon normal H_2O_2 production linked in turn to normal oxidative metabolism How steroids inter fere is not clear and relatively high doses are needed to produce similar alterations in vitro (5 14) Decreased bactericidal capacity of neutrophils is however also noted during the stress of extensive burns (1) and infection (12)

In conclusion treatment with prednisone in mod erate doses besides having a striking clinical effect in many cases modifies several laboratory para meters of inflammatory and immune functions while others remain unchanged To what extent these findings are relevant for the clinical response is not known Our results are however compatible with the notion that a major part of the clinical effect of prednisone is due to suppression of the inflammatory part of the immune response

ACKNOWLEDGEMENTS

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Iron Absorption in Patients with Chronic Uremia Undergoing Regular Hemodialysis

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ABSTRACT Gastrointestinal iron absorption has been measured by whole body counting in 17 patients with chronic uremia undergoing regular hemodialysis Absorption was expressed as whole body retention 14 days after oral administration of 10 μCi ^{59}Fe together with a carrier dose of 10 mg Fe^{2+} The percentage incorporation in the total erythrocyte mass of administered ^{59}Fe (erythrocyte incorporation) and absorbed ^{59}Fe (red cell utilization) was estimated as well Geometric mean iron absorption was 14 3±2 0 (S D)% and significantly higher than the value obtained in a normal control group ($p<0\ 03$) Geometric mean erythrocyte incorporation was 11 6±2 3 (S D)% and arithmetic mean red cell utilization was 84 4±6 0 (S E M)% Neither of these parameters differed from corresponding values in the control group ($p>0\ 1$ and $p>0\ 2$ respectively) The correlation between iron absorption and erythrocyte incorporation was highly significant ($r=0\ 94$, $p<0\ 001$) Patients on regular hemodialysis are subjected to considerable iron loss which should be treated by iron supplementation oral iron administration is recommended in view of the adequate gastrointestinal absorption

The uremic condition is almost invariably accompanied by a more or less pronounced anemia which in the predialytic stage is usually of slight degree neither restricting physical activities nor requiring blood transfusions (31) During regular dialysis treatment (RDT) the anemia is accentuated and becomes a prominent therapeutic problem influencing the well being and working capacity of the patients

Primarily the anemia emerges from a deficient erythropoiesis due to insufficient production of renal erythropoietic stimulating factor (2 12 15) Other reasons are a reduced red blood cell life span (2 5 15) and a considerable blood loss in connection with dialyses and blood sampling (3 5 20) Marrow depression by uremic toxins should also be taken into account as dialytic therapy improves the rate of erythropoiesis (2 14 24)

Erythropoietic stimulating factor is not available for clinical use and regular blood transfusions which used to be regarded as inevitable in RDT (11) have now been abandoned as a routine treatment of the anemia as a consequence of their clear disadvantages (7 14 22 30) The therapeutic measures have been aimed instead at blood saving procedures and at providing optimal conditions for erythropoiesis by securing adequate supplies of factors necessary in Hb formation including iron The appreciable iron loss in RDT makes great demands on gastrointestinal absorptive capacity

Previous investigations on this subject have yielded contradictory results (3 5 7 13 26) and the present study was undertaken to reexamine gastrointestinal iron absorption in patients undergoing RDT and assess whether oral iron therapy alone is sufficient to maintain the iron balance or whether parenteral iron supplementation is indicated

PATIENT MATERIAL

Seventeen patients (12 males 5 females) participated in the study Further data are given in Table I All had a 24 hour endogenous creatinine clearance of ≤0 1 ml/min and had been on dialytic treatment during 1–49 months (mean 23) Dialysis was performed for 8 to 10 hours twice weekly using the Gambro-Lundia® artificial kidney All patients were taking a protein sodium- and potassium restricted diet containing an average of 0 9 g protein/kg b wt /day together with vitamin supplements except fo-

Table I. *Clinical, renal and hematological data on 17 patients on regular hemodialysis investigated for iron absorption*

Pat. no.	Sex	Age (y)	Diagnosis	Serum creatinine (mmol/l)	Serum urea (mmol/l)	Serum B_{12} (pmol/l)	Erythrocyte folate (nmol/l)	Erythrocyte glucose-6-phosphate dehydrogenase (U/mean erythrocyte)
1	♂	23	Hereditary nephropathy (Alport)	1.21	28	592	206	318
2	♂	52	Chronic glomerulonephritis	0.90	29	599	480	253
3	♂	28	Chronic glomerulonephritis	1.70	32	651	(2 300)	507
4	♂	32	Chronic glomerulonephritis	1.60	27	703	340	329
5	♂	26	Chronic glomerulonephritis	1.60	37	903	–	403
6	♂	55	Nephrosclerosis	1.39	34	511	415	335
7	♂	32	Chronic glomerulonephritis	1.72	35	629	492	212
8	♂	54	Chronic glomerulonephritis	1.18	32	303	737	550
9	♂	36	Chronic glomerulonephritis	1.65	30	477	723	344
10	♂	39	Polycystic kidneys	1.34	23	444	195	198
11	♂	54	Chronic pyelonephritis	1.26	18	348	567	365
12	♂	42	Bilateral nephrectomy (nephrosclerosis)	1.54	44	688	610	320
13	♀	38	Chronic glomerulonephritis	1.41	30	950	197	375
14	♀	38	Chronic glomerulonephritis	1.67	33	340	807	471
15	♀	36	Primary hyperoxaluria	1.22	36	548	665	346
16	♀	35	Bilateral nephrectomy (acute glomerulonephritis)	0.95	27	510	326	274
17	♀	50	Bilateral nephrectomy (polycystic kidneys)	1.24	29	385	425	319
Arithmetic mean		39		1.39	31	564	449	341
S.D.		10		0.26	6	183	230	92
Normal				≤0.13	≤7.5	140–600	247–665	205–320

late which was given to only one patient (no. 3). Aluminium aminoacetate was administered in order to correct hyperphosphatemia. None of the patients had been [illegible]jected to gastrointestinal surgery or had clinical signs [illegible]mination or infection; four females were men[illegible]

[illegible] patients had negative Coombs' test and normal [illegible]rum bilirubin. In 13 patients achlorhydria was excluded by the pentagastrin test. Blood sampling was restricted to a minimum, biochemical monitoring being made once or twice monthly. Blood transfusions were avoided as a routine, but two nephrectomized patients (nos. 16 and 17) required regular transfusions, which were withheld 2 weeks before and during the investigation.

Most patients received peroral iron therapy as ferrous fumarate 200 mg (66 mg elemental Fe^{2+}) together with ascorbic acid 250 mg thrice daily; this treatment was discontinued at least 2 weeks before and during the iron absorption test.

METHODS

Iron absorption was measured by whole body counting—using the whole body monitor—by the method described in a previous paper (25). All non-vital medicine including aluminium aminoacetate was withheld for 4 days before the study and blood sampling was avoided in the investigation period. Measurements of the whole body ^{59}Fe activity were performed at 4 hours and 14 days after the oral administration of 10 μCi ^{59}Fe together with 9.9 mg Fe^{2+} (as sulphate) as carrier to the fasting subject and corrected for background and radioactive decay before calculation of the percentage absorption of iron. Erythrocyte volume was estimated according to the method described by Jarnum (23) and at the last counting procedure blood samples were drawn in order to assess the ^{59}Fe activity. From these measurements were calculated the erythrocyte iron incorporation (EIC), i.e. the percentage of administered ^{59}Fe recovered in the total erythrocyte mass, and red cell utilization, i.e. the percentage of absorbed ^{59}Fe recovered in the erythrocytes.

Hb values were calculated as the averages of pre- and postdialytic measurements within two months before the study and serum creatinine and serum urea were taken as the averages of predialytic values in the same period.

Hematological parameters including Hb, mean corpuscular volume (MCV), mean corpuscular Hb concentration (MCHC), hematocrit, serum iron, plasma transferrin, plasma total iron binding capacity (TIBC), erythrocyte glucose-6-phosphate dehydrogenase, erythrocyte folate and serum vitamin B_{12} were estimated by procedures described earlier (25, 31) and reticulocyte counts were corrected for anemia (35).

Bone marrow specimens were obtained by iliac crest

Table II *Hematological data iron absorption and erythrocyte incorporation in 17 patients on regular hemodialysis*

Pat no	Hb (mmol/l)	Corrected reticulocyte count (1/1000)	MCHC (mmol/l)	MCV (fl)	Serum iron (μmol/l)	Plasma transferrin (μmol/l)	Plasma TIBC (μmol/l)	Transferrin saturation (%)	Marrow iron (0–4+)	^{59}Fe absorption (%)	EIC (%)
1	6 1	16	20 4	89	9 3	26 8	53 6	17 4	2+	16 3	11 0
2	4 5	6	20 5	89	15 1	25 6	51 2	29 5	1+	8 7	7 7
3	2 6	12	21 8	102	16 5	32 7	65 4	25 2	2+	20 6	18 3
4	3 2	9	19 3	102	33 4	23 4	46 8	71 4	1+	9 6	5 7
5	2 1	18	19 0	91	35 6	21 7	43 4	82 0	2+	5 3	5 7
6	3 4	21	18 8	102	9 8	27 6	55 2	17 8	1+	46 4	35 0
7	4 6	9	20 0	87	17 3	22 2	44 4	39 0	2+	7 0	5 5
8	3 0	18	19 5	98	9 6	29 8	59 6	16 1	2+	18 4	18 3
9	4 5	31	21 0	95	21 8	23 5	47 0	46 4	1+	25 4	22 9
10	4 4	18	20 3	90	8 8	22 3	44 6	19 7	2+	15 4	10 0
11	3 3	25	20 0	108	15 5	26 8	53 6	28 9	0	18 9	20 6
12	3 1	1	21 8	90	17 3	20 3	40 6	42 6	1+	5 0	3 6
13	3 7	15	20 1	98	16 9	28 8	57 6	29 3	0	9 4	12 5
14	2 9	21	22 0	91	14 1	34 4	68 8	20 5	0	21 2	19 5
15	5 4	27	21 5	82	12 3	39 9	79 8	15 4	1+	54 4	64 6
16	4 2	12	21 7	101	36 4	21 0	42 0	86 7	–	5 9	2 6
17	2 7	3	20 0	97	14 3	20 3	40 6	35 2	3+	70 6	9 4
Arithmetic mean	3 8	15	20 5	95	17 9	26 3	52 6	36 7		18 1	16 1
S D	1 1	8	1 0	7	8 9	5 5	11 0	22 8		13 8	15 1
Geometric mean										14 3	11 6
S D										2 0	2 3
Normal range	7 0–10 5	<12	18 6–22 3	81–109	10 7–34 0	24 2–47 7	48 4–95 4			1 9–38 3	1 6–37 0[a]

[a] Larsen & Milman (25)

puncture stained for iron with Prussian blue whereafter the iron content was graded according to Rath and Finch (33) The Institute of Pathology Rigshospitalet provided with help and advice in the technical preparation and assessment of the marrow aspirates and liver biopsies In 3 patients the stainable liver iron content was assessed as well

The control group consisted of 27 healthy subjects Details concerning this group have been reported in a previous publication (25)

Logarithmic transformation of the values for iron absorption and EIC was performed and employed in the calculation of the geometric mean according to Cook et al (9)

In the statistical analysis regression lines were calculated according to the method of least squares and the Mann Whitney rank sum test was used to evaluate significant differences between patients on RDT and controls

RESULTS

Clinical hematological and biochemical data together with values for iron absorption and EIC are shown in Tables I and II

Iron absorption and erythrocyte incorporation of ^{59}Fe

In the patients iron absorption ranged from 5 3 to 54 4% with an arithmetic mean of 18 1±13 8 (S D)% (Fig 1) and a geometric mean of 14 3±2 0 (S D)% EIC ranged from 2 6 to 64 6% with a geometric mean of 11 6±2 3 (S D)% Red cell utilization of absorbed ^{59}Fe averaged 84 4±6 0 (S E M)% (arithmetic mean) 15 patients had values above 60% while the two patients who received regular transfusions had values around 45%

The control group had an arithmetic mean iron absorption of 11 5±10 4 (S D)% and a geometric mean absorption of 8 5±2 1 (S D)% Geometric mean EIC was 7 7±2 2 (S D)% while arithmetic mean red cell utilization was 92 9±4 0 (S E M)% (25)

Iron absorption was higher in the patients compared to the controls ($p<0$ 03) while EIC and red cell utilization showed no significant difference ($p>0$ 1 and $p>0$ 2 respectively)

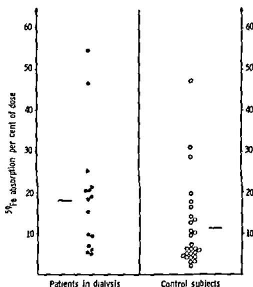


Fig 1 Absorption of ^{59}Fe in patients undergoing regular hemodialysis and in controls

The correlation between iron absorption and EIC was highly significant in patients ($r=0.94$ $p<0.001$) and in controls ($r=0.96$ $p<0.001$) as shown in Fig 2

The iron absorption demonstrated a negative correlation with the transferrin saturation ($r=-0.54$ $p<0.05$) (Fig 3) while a positive correlation was found against the TIBC ($r=0.66$ $p<0.01$) (Fig 4)

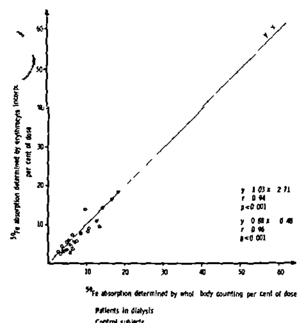


Fig 2 Relation between iron absorption and erythrocyte incorporation of ^{59}Fe

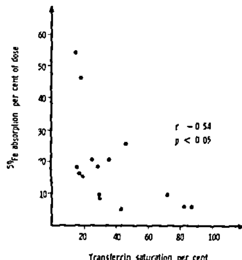


Fig 3 Relation between transferrin saturation and iron absorption in dialysis patients

and the corrected reticulocyte count ($r=0.59$ $p<0.05$) (Fig 5)

We failed to demonstrate any correlation between iron absorption and serum iron the degree of uremia or the duration of dialytic therapy

Hematological studies

The uremic patients had a normocytic and normochromic anemia The corrected reticulocyte counts were significantly higher in the patients than in the controls ($p<0.03$)

Bone marrow examinations revealed normoplastic or slightly hyperplastic marrows with nor

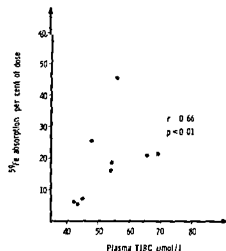


Fig 4 Relation between plasma total iron binding capacity (*TIBC*) and iron absorption in dialysis patients

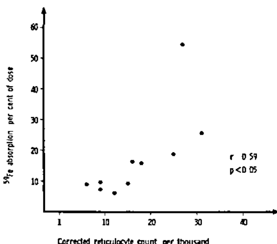


Fig 5 Relation between corrected reticulocyte count and iron absorption in dialysis patients

moblastic erythropoiesis The stainable marrow iron content was assessed as normal or increased in 7 patients reduced in 6 and absent in 3 There was a discrepancy between stainable marrow and liver iron content liver iron was abundant (patients 2 and 12) or excessive (patient 17 had hepatic hemosiderosis) in spite of reduced or normal marrow iron (Table I)

Biochemical studies

The serum iron and transferrin saturation exhibited considerable variations Both these parameters and the TIBC seemed to be unsatisfactory guides to the state of the iron stores as indicated by the bone marrow studies Thus it appears from Tables I and II that subnormal serum iron values (patients 1 6 8 10) can co exist with normal or slightly reduced iron stores while exhausted iron stores are not necessarily reflected in a low serum iron (patients 11 13 14)

The plasma transferrin was lower in the patients than in the controls ($p<0\ 002$) The serum B_{12} measurements revealed normal or supranormal values in all patients and the erythrocyte folate values were within the normal range

The erythrocyte glucose-6-phosphate dehydrogenase was generally supranormal (10 patients) or in the upper half of the normal range (4 patients) only 3 patients had values in the lower half of the normal range

DISCUSSION

Patients on RDT are subjected to a substantial blood loss (3 5 20 27) mainly dependent on the type of the artificial kidney employed the frequency of dialyses and the extent of blood sampling for biochemical investigation and research The calculated *minimum* blood loss in the present investigation was per annum in each patient 2 50 l (average Hb content 3 8 mmol/l) equivalent to 530 mg iron which together with the obligatory iron losses (1 mg/day in males 2 mg/day in females) gave a total annual iron loss of 895 mg in males and 1 260 mg in females Thus the maintenance of iron balance necessitates a daily absorption of at least 3–4 mg iron

Gastrointestinal iron absorption in patients on RDT has been investigated previously (Table III)

Table III *Iron absorption values from the literature in patients undergoing regular hemodialysis*
WBC = whole body counting

				^{59}Fe absorption (% of dose)		
Authors	No of subj	Method	Carrier dose	Arithmetic mean	Range	Significant difference from control subjects
Comty et al (7)	10	Fecal recovery	None	51 0	44 0–88 0	Yes higher
Eschbach et al (13)	32	Double isotope	5 mg Fe^{2} as sulphate	31 2	1 0–100	No
Blumberg & Chappuis (3)	12	WBC	4 mg Fe^{2} as sulphate	4 4±1 4 (S D)	1 4– 6 3	Yes lower
Brozovich et al (5)	13	WBC	5 mg Fe^{2} as sulphate	21 5	5–65	No
Lawson et al (?6)	1?	WBC	5 mg Fe as chloride	? 0+0 5 (S E M)	0 2– 5 4	Yes lower
Present study	1	WBC	10 mg Fe^{2} as sulphate	18 1+13 8 (S D)	5 3–54 4	Yes higher

Several authors (5 7 13) have demonstrated that the iron absorption in uremic patients is normal depending on the iron balance being low in iron overloaded and high in iron deficient subjects

Other investigators (3 26) have found a depressed iron absorption in patients on RDT Thus the series of Lawson et al (26) has the lowest iron absorption reported and the authors suggest that this finding could be secondary to decreased erythropoiesis as indicated by the extremely low utilization of i v ^{59}Fe The failure of parenteral iron therapy to produce a rise in hematocrit provided indirect support for this assumption

The present results demonstrate that patients on RDT have preserved the ability to adapt iron absorption to the demands of erythropoiesis and *that iron deficiency can be prevented by the* administration of oral iron supplementation which is necessary in view of the low iron content of the protein restricted diet (31) and the less favourable absorptive conditions created by a diet poor in meat products (8 29) If the iron loss is extensive absorption can be improved by the administration of iron between meals together with ascorbic acid (8 19 21)

Estimation of the EIC was intended as a control on the iron absorption and the close correlation between these parameters (Fig 2) supports the validity of the absorptive results

Both the high corrected reticulocyte count and increased erythrocyte glucose-6-phosphate dehydrogenase are indicative of a young erythrocyte population (37) and suggest a decreased red cell life span due to either hemolysis and/or blood loss (2 5 15)

The utilization of absorbed ^{59}Fe was slightly but not significantly lower in patients than in controls and of the same order of magnitude as reported earlier (5)

Plasma transferrin values are low in patients on RDT (32 34) whether this is caused by decreased synthesis or increased catabolism or losses is still unclear

The present results show a connection between the iron balance (judged by transferrin saturation and plasma TIBC) and iron absorption (Figs 3 4) It has been demonstrated that the degree of saturation of transferrin influences the extent of iron absorption under certain conditions (17 18 36) This relationship is most distinct at the extremes of iron balance representing deficiency and overloading (13) but is not demonstrable in subjects with normal iron balance (25) Similar considerations are probably valid for the relationship between TIBC and iron absorption (4 25)

None of our patients were clearly iron deficient (28) but four were probably iron overloaded (nos 4, 5 16 17) Hyperabsorption of iron also occurs as demonstrated by the high absorption in patient 17 in spite of abundant iron stores

The assessment of iron content by histochemical methods in marrow aspirates and liver biopsies is semiquantitative and encumbered with several sources of errors and the poor correlation against serum iron TIBC and transferrin saturation found in the present study has been confirmed by others (3, 10)

The discrepancy between stainable marrow iron and liver iron has been observed in other patients (Milman unpublished data) and suggests an increased hepatic accumulation of iron possibly caused by an abnormal hepatic handling involving increased uptake (15 16) and/or hampered release from hepatic cells

There is evidence that the release of reticuloendothelial iron is impaired in chronic renal failure (1) this could be responsible for the high absorption observed in many of the patients despite the presence of stainable marrow iron

Several authors (3 6 22) advocate parenteral iron therapy as a routine in connection with dialysis but in view of the excellent gastrointestinal absorption this is only indicated when absorption is compromised due to some gastrointestinal disorder Iron loss is inevitable in RDT but should be kept to a minimum primarily by restriction of blood sampling The low dietary iron content makes oral iron therapy mandatory in order to maintain a favourable iron balance

ACKNOWLEDGEMENTS

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The Effect of Indomethacin on Proteinuria and Kidney Function in the Nephrotic Syndrome

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ABSTRACT In 19 nephrotic patients on a dietary intake of 20 mEq sodium/24 hours indomethacin caused an immediate decrease in glomerular filtration rate (GFR) and urinary protein excretion an effect completely reversible upon withdrawal of the drug As a consequence of lower protein excretion there was eventually a rise in GFR It is proposed that the therapeutic effect of indomethacin in nephrotic syndrome is caused by its inhibiting action on renal prostaglandin synthesis, thereby potentiating the effect of the renin angiotensin system on the kidney The difference between the decrease in GFR (mean 35%) and proteinuria (mean 55%) and the more selective proteinuria during indomethacin administration may be explained by quantitative and qualitative differences in protein leakage between outer cortical and inner cortical nephron populations

In patients with nephrotic syndrome indomethacin may cause a reduction of urinary protein excretion (4 11 12 13) Recently we have shown (15) that the glomerular filtration rate (GFR) decreases during administration of this drug to volunteers with a normal or reduced kidney function without proteinuria The sodium and water retention and the larger decrease in GFR on a sodium restricted diet support the hypothesis that these effects of indomethacin are the result of a potentiation of the renin angiotensin system by the inhibitive action of indomethacin on prostaglandin synthesis (1 8 9) These results in the non proteinuric state raised the possibility that the decrease in proteinuria which accompanies indomethacin administration in nephrotic syndrome is caused by diminished glomerular filtration This was tested in 19 patients with a nephrotic syndrome It was observed that indomethacin induces a rapid decrease in proteinuria invariably associated with an initial fall in GFR Both effects were enhanced by a sodium restricted diet and immediately reversible when the drug was discontinued

We suggest that indomethacin influences protein excretion by changing intrarenal hemodynamics

PATIENTS AND METHODS

Nineteen patients with proteinuria of 5 0 g or more (Fig 1) and serum albumen concentrations of 3 0 g/100 ml or less were studied Eleven of them were males and eight females with a mean age of 30 years (range 14–56) Based upon kidney biopsy their diagnoses were membranous nephropathy 7 focal glomerulosclerosis 6 membranoproliferative glomerulonephritis 2 diffuse diabetic glomerulosclerosis 1 amyloidosis 1 minimal lesions (in a patient with gold therapy for his rheumatoid arthritis) 1 transplant kidney without characteristic glomerular changes 1

All patients were studied during hospitalization They received a diet containing 20 mEq sodium a day Indomethacin 150 mg a day was given orally in three divided doses The patients were not treated with corticosteroids nor with immunosuppressive agents Observations were made in the week before and within a week after the start of indomethacin medication (Fig 1) Additionally before instituting long term indomethacin administration in 10 of the 19 patients the drug was given for three days only while proteinuria and kidney function were measured in the three days preceding during the three days of indomethacin administration and in the three days immediately following withdrawal of the drug (Fig 2)

Effective renal plasma flow (ERPF) and GFR were measured simultaneously by ^{131}I-hippuran (Philips Duphar) and ^{125}I sodium iothalamate (Radiochemical Centre Amersham) (5 6) Protein in urine was measured by the biuret method The selectivity of proteinuria was esti

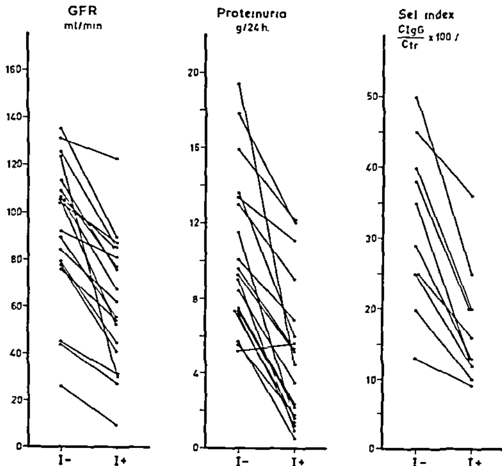


Fig. 1. GFR, proteinuria (mean of three consecutive days) and selectivity index before (*I*−) and during (*I*+) indomethacin administration.

as IgG clearance/transferrin clearance × 100% ac... to Cameron and Blandford (2). The coefficient of ... of this method was 12%. IgG and transferrin concentrations in serum and non-concentrated 24-hour urine samples were estimated by radial immunodiffusion (10) (Partigen, Behring Werke, Marburg).

RESULTS

Administration of indomethacin resulted in a lowering of the GFR in all patients (Fig. 1). The ERPF decreased in 16 of the 19 patients (mean 23%) and the filtration fraction (FF) also in 16 (mean 17%). Proteinuria decreased in all patients except one (Fig. 1). These effects were apparent within 24 hours, as was their disappearance upon discontinuation of the drug (Fig. 2).

The overall mean percental decrease in proteinuria (55%, S.D. 27%) exceeded the mean percental decrease in GFR (35%, S.D. 17%) ($p<0.02$, Student's *t* test). In three of the 19 patients, however, the reverse was observed and in two of these three the advantage of a lower protein excretion did not outweigh clinically the loss of renal function, so the treatment was interrupted. Treatment was also discontinued in the only patient in whom proteinuria remained unchanged during indomethacin administration and in two others because of a too large reduction of GFR (65% and 76%). A result justifying prolonged treatment was therefore obtained in 14 patients. Of these, five had residual proteinuria of more than 5 g a day, the other nine responded to such a degree that proteinuria was below this level (Fig. 1). No relation was observed between response to indomethacin and histological diagnosis.

In the patient without reduction of proteinuria and in one of the patients with an insignificant reduction, indomethacin was administered again

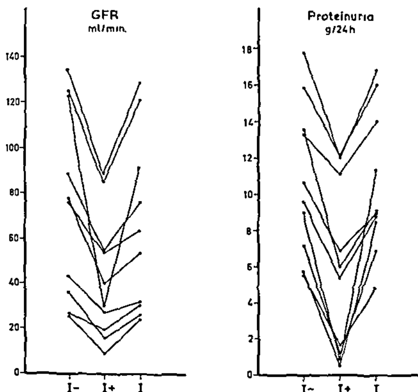


Fig 2 GFR and proteinuria (mean of three consecutive days) before (*I*−) during (*I*+) and after (*I*) indomethacin administration

one year later when renal function had decreased due to progression of the disease In this stage an evident decrease in proteinuria was observed (Table I)

In 10 patients selectivity of proteinuria was estimated before and during indomethacin administration (Fig 1) Proteinuria became more selective in all of them

The effect of discontinuing indomethacin treatment after 1–2 years of administration was tested in three patients It consisted of an immediate rise in GFR and urinary protein excretion (Table II)

In three patients in whom sodium intake was stepped up to 100 mEq a day during indomethacin treatment proteinuria increased to pretreatment levels (from 3 5 to 8 5 g/24 h from 2 5 to 5 8 g/24 h and from 2 9 to 7 1 g/24 h)

DISCUSSION

In patients with a nephrotic syndrome maintained on a sodium restricted diet indomethacin induced a rapid fall in GFR together with a decrease in ERPF and FF This effect was immediately reversible

Table I *GFR (ml/min) and proteinuria (g/24 h) before (I−) and during (I+) indomethacin medication in two patients at an early stage of the disease and one year later*

Percental decrease within parentheses

	Early stage				1 year later			
	GFR		Proteinuria		GFR		Proteinuria	
Diagnosis	*I*−	*I*+	*I*−	*I*+	*I*−	*I*+	*I*−	*I*+
Diabetic glomerulosclerosis	135	89 (34)	15 9	12 2 (23)	60	47 (25)	25 0	12 0 (52)
Amyloidosis	131	122 (7)	5 6	5 4 (0)	108	77 (29)	11 6	3 8 (67)

Table II *GFR and proteinuria in three patients after 1–2 years of administration (I+) upon discontinuation (I−) and after reinstitution (I) of indomethacin*

Pat no	GFR (ml/min)			Proteinuria (g/24 h)		
	I+	*I−*	*I*	*I+*	*I−*	*I*
1	58	90	60	0.7	4.7	0.6
2	39	46	34	6.2	14.0	7.1
3	34	46	33	4.1	11.5	1.8

upon withdrawal of the drug both after a short period of administration and after several years Similar changes in kidney function have been observed in volunteers with normal or reduced GFR without proteinuria (5) In the nephrotic patients studied here a decrease in urinary protein excretion coincided with the fall in GFR and was likewise reversible upon discontinuation of indomethacin administration This observation suggests that the decrease in protein leakage in the kidney could be the consequence of the lowered GFR

There is ample evidence that intrarenal blood flow is largely dependent upon the equilibrium between the activity of the renin angiotensin system on the one hand and the prostaglandin system on the other (1 8 9) Dietary sodium restriction will enhance the activity of the former and indomethacin will inhibit the activity of the latter system This will result in a decrease in renal blood flow and leading at the same time to a lowered clear of serum proteins The observation in this that ERPF was less affected than GFR is probably a consequence of a higher hippurate extraction in the kidney during indomethacin medication (5)

The decrease in proteinuria by indomethacin disappeared when the dietary sodium intake was increased from 20 to 100 mEq a day Apparently indomethacin can only exert its action on proteinuria when the renin angiotensin system is stimulated

The individual percental decrease in GFR during indomethacin administration showed wide variability In part these differences may have been the consequence of different plasma levels of indomethacin as a standard dose of indomethacin was administered irrespective of body weight and renal function

The prostaglandin system in particular is capable of increasing the blood flow through inner cortical nephrons probably by a vasodilating effect on the efferent arterioles of these glomeruli (1 8 9) This could explain the difference in percental decrease between GFR and urinary protein excretion during indomethacin administration as being based on quantitative differences in protein leakage between inner cortical and outer cortical nephron populations Furthermore the greater selectivity of proteinuria may indicate that there are also qualitative differences in permeability between the glomeruli in the inner and outer cortex

Although several authors have observed a fall in creatinine clearance during indomethacin medication of patients with a nephrotic syndrome a rise in creatinine clearance has been reported too (12 13) This may be explained by the gradual rise in serum albumen concentration during indomethacin treatment which follows the decrease in proteinuria A rise in serum albumen concentration may change GFR in two opposing ways Firstly GFR may decrease because of an increased oncotic pressure secondly and probably more important GFR may increase due to the expansion of the plasma volume In nephrotic syndrome of recent onset for example in the minimal change group plasma volume tends to be low owing to the acute hypoproteinemia In its extreme form this may even lead to acute renal failure (3) When a remission is obtained with corticosteroid treatment there is not only a rise in serum albumen concentration but this is accompanied by a parallel increase in GFR This was found in our series of 12 patients with minimal change disease (r=0.82) (unpublished observations) and a similar correlation may be calculated from the data of Hopper et al (7) in 31 such patients (r=0.64)

In the present patient group little benefit was to be expected from corticosteroids or immunosuppressive agents In the majority of these patients a clinically important decrease in proteinuria was obtained by indomethacin administration in combination with a sodium restricted diet The way the underlying disease process is influenced by long term indomethacin medication should be the subject of further study probably in the first place in animal models

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Importance of Season and Clearance Correction in the Definition of Hypercalciuria

Preliminary Report

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The urinary excretion of calcium derives from the complex interplay of the factors influencing the filtered load and the tubular handling of this ion Obviously in order to define hypercalciuria the dietary intake of calcium has to be controlled (5) and the inter and intraindividual variations in the clearance of creatinine must be corrected (4 6 9 10 11) As a matter of fact without this correction hypercalciuria may even be undetectable in idiopathic renal stone formers studied on a free diet (1) But one must also consider the possibility of additional variables The recent observation of rather marked seasonal variations in the plasma level of the intermediary vitamin D_3 metabolite 25 hydroxy cholecalciferol (25 OHCC) (2 8) suggests that part of the normal variability in the renal excretion of calcium may be season related To elucidate this problem we undertook the present pilot study of the seasonal variations in the *clearance corrected* renal calcium excretion of healthy volunteers taking a *standard* diet

MATERIAL AND METHODS

A group of 26 persons (nurses and medical students) 9 females (aged 20–54 years average 34) and 17 males (aged 21–29 years average 24) served as healthy volunteers taking for five days a standard diet with the estimated contents of 800 mg calcium 900–1100 mg phosphorus and 60–140 mEq sodium per day and 1 g protein/kg b wt /day One group of volunteers (5 females and 7 males) were studied during the summer (May–Sept inclusive) and the remaining 14 during the winter (Oct –April inclusive) In addition the five females studied in May to July had their studies repeated in Feb –March of this year Urine was collected on a 24-hour basis on all five days and the specimens from the 4th and 5th days were analyzed for calcium sodium and creatinine Daily determinations of serum total calcium (TOCa) and creatinine were carried out on the 4th–6th day Average values were used for the determination of the 24-hour urinary calcium excretion (UCaV mg/24 h) and sodium excretion (UNaV mEq/24 h) the 24-hour clearance of creatinine (CCr ml/min) and for correction of the renal calcium excretion for clearance variations according to the formula (UCaV× 100)/CCr The 24-hour urinary excretion of creatinine (UCrV mg/kg b wt /24 h) was used as a measure of lean body mass (3) The analytical methods will be described elsewhere (11)

RESULTS

Although the winter group had a larger lean body mass and correspondingly higher CCr values it tended to have the lowest values of *uncorrected* UCaV (Table I) Correction for clearance differences accentuated this summer to-winter difference which turned out to be statistically significant ($p<0.01$) (Table I) Fig 1 reveals a distinct seasonal variation in the clearance-corrected renal excretion of calcium with an increase in the monthly average from a nadir in Feb to a zenith in July followed by a corresponding decrease to a low in Dec This pattern was readily recognizable even when males and females were considered separately The five females who had clearance-corrected UCaV values of 320 258 252 179 and 168 mg/24 h during the summer exhibited decreases of 36 15 13 12 and 10% respectively during the winter This change took place without any change in CCr 92 against 91 ml/min and despite some increase in the clearance corrected UNaV averaging 47 mEq/24 h

DISCUSSION

The importance of paying attention to the diet and to the CCr during evaluation of the renal excretion of calcium is well documented (1 4 5 6 9 10 11) When these precautions are taken as in the present study results indicate a significant *summer to winter* difference in the reference

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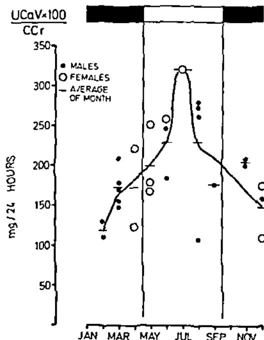


Fig 1 Seasonal pattern in the clearance-corrected urinary excretion of calcium observed in 26 healthy volunteers taking a *standard* diet

interval (mean ±2 S D) of the *clearance corrected* renal excretion of calcium of 103–347 mg/24 h during the summer against 91–239 mg/24 h during the winter The reality of this summer to-winter difference was substantiated by repeating the studies in five persons These studies suggest that those exhibiting the highest summer values also experience the largest decrements during the winter

- all persons in the present pilot study were taking a *standard* diet these results indicate that the seasonal variations in the daily UCaV which were noticed recently in persons taking a *free* diet (7) cannot be explained solely *by seasonal variations in the dietary intake of calcium* The most likely explanation of the difference found is seasonal variations in endogenous vitamin D_3 generation (2 8) Studies of the relationship between the present observation and variations in the serum levels of 25 OHCC and immunoreactive parathyroid hormone are in progress

The bearing of the present investigation on the definition of hypercalciuria and on the evaluation of drugs given with the intention of treating disorders of calcium metabolism is obvious and has to be considered in future studies

Table I *Seasonal intergroup differences in lean body mass glomerular filtration rate and the urinary excretion of sodium and calcium (mean±S D)*

	Summer	Winter	Probability of differences[a]
No of volunteers	12 (7 ♂ 5 ♀)	14 (10 ♂ 4 ♀)	
UCrV(mg/kg/24 h)[b]	20 9±3 3	25 0±2 8	<0 01
CCr *(ml/min)*	*103±19*	*121±13*	*<0 01*
UNaV (mEq/24 h)	92±38	108±36	>0 10
UNaV×100 / CCr	92±36	91±33	>0 10
TOCa (mg/100 ml)	9 84±0 38	9 94±0 34	>0 10
UCaV (mg/24 h)	230±66	199±47	>0 10
UCaV×100 / CCr	225±61	165±37	<0 01

[a] By Student s *t* test [b] As measure of lean body mass (3)

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Diagnosis and Treatment of Acute Gastrointestinal Haemorrhage in a Small District Hospital

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ABSTRACT Ninety-eight consecutive patients admitted to a small district hospital because of acute gastrointestinal haemorrhage have been studied Patients with haematemesis and/or melaena were treated with antacids and tranexamic acid from the very beginning and were examined with early panendoscopy All patients were closely observed in an ordinary medical ward by a staff especially trained to handle acute gastrointestinal bleeding Seven patients required acute surgery The overall mortality was 4 1% It is concluded that acute gastrointestinal haemorrhage can be successfully handled with modern diagnosis and treatment in a small hospital

Acute gastrointestinal haemorrhage especially when massive continues to be a medical emergency with a considerable mortality especially in the aged (9) To date results of diagnosis and treatment of such haemorrhage have been published by groups working in large hospitals only The present study therefore was undertaken in order to evaluate the results of modern diagnosis and treatment of acute gastrointestinal bleeding in a small district hospital

PATIENTS AND METHODS

Our hospital serves a population of 54 000 and has an annual turnover of 4 500 in patients in the Departments of Internal Medicine and Surgery It has no intensive care unit except one for coronary care The present study includes all patients admitted to the hospital between Sept 1 1973 and Aug 31 1974 because of acute gastrointestinal haemorrhage except those who despite a history of haematemesis or melaena had no fall in their Hb level and no positive test for Hb in the faeces Altogether 98 patients 63 males and 35 females were admitted because of verified acute gastrointestinal haemorrhage The age distribution is shown in Table I Of the patients 53% were more than 60 years old 12% being more than 80 Haematemesis and/or melaena was the presenting symptom in 93% the remainder presented with passage of red blood per anum

All patients were treated in an ordinary medical ward the staff of which had been specially trained in the management of acute gastrointestinal bleeding The patient were closely observed day and night by nurses and attendants who were especially alert to signs of insufficient peripheral circulation Urine output per hour was followed in all cases of moderate or severe bleeding Gastric aspiration was performed in cases with severe haematemesis only

Of the 91 patients admitted because of haematemesi and/or melaena 48% had an initial or minimum Hb level of less than 8 9 g/100 ml 33% had a corresponding level of 9–11 9 g/100 ml and the remaining 19% retained the Hb level above 12 0 g/100 ml during the entire stay in the hospital Of these patients 11 showed clinical signs of shock or preshock on admission or later during the hospitalization Of the 7 patients admitted because of passage of red blood per anum 3 had a lowest Hb value of 9–11 9 g/100 ml and the remaining 4 did not bleed to values below 12 0 g/100 ml None of these patients showed clinical signs of shock at any time during the hospital stay

Volume loss was substituted with saline and glucose infusions and blood transfusions were given on strict indications only these being more liberal in elderly patients and in patients with known coronary or cerebral arterial insufficiency All patients except those with minimal haemorrhage were given 3 g daily of the antifibrinolytic agent tranexamic acid (Cyklokapron ® Kabi) parenterally for 3 days and then orally for another 3 days Antacids (Novalucol forte Hassle) were given from the beginning to all patients with haematemesis and/or melaena

Blood transfusions were given to 46 of the 98 patients

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Table I *Age distribution of 98 patients with verified acute gastrointestinal haemorrhage*

Age (y)	No of pats
<20	1
20–29	5
30–39	8
40–49	8
50–59	24
60–69	19
70–79	21
>80	12

In the remaining cases the anaemia was treated with oral or parenteral iron only The indications for acute surgery were determined jointly by the responsible physician and surgeon from case to case

The initial diagnostic manoeuvre in 62 of the 91 cases with haematemesis and/or melaena was early endoscopy of the distal oesophagus stomach and duodenum performed within 1–7 days of admission An Olympus JF Type B was used The distal oesophagus was examined by careful bending of the distal portion of the instrument enabling the examiner to get a forward view of the oesophagus During duodenoscopy 0 2 mg of glucagon (Glucagon Novo) were given i v only in cases with very active peristalsis in order to relax the duodenum and facilitate the view A barium meal examination was done after endoscopy in 8 of these 62 patients as well as in 5 of the 29 patients not subjected to endoscopy In the remaining 24 cases neither endoscopy nor barium studies were performed

Rectoscopy with a conventional stiff instrument was performed in all 7 cases with red rectal bleeding A barium enema examination was done in 4 and fibreoptic coloscopy with Olympus CF MB 2 in 2 of these cases

RESULTS

Diagnostic efforts

Haematemesis and/or melaena Early endoscopy gave a diagnosis of bleeding or potentially bleeding lesions in 50 cases In 12 cases no definite lesion could be found Table II shows the type of lesions found and Table III the location of these lesions No complications of endoscopy occurred

A barium meal examination in 8 of the patients examined with endoscopy did not give any additional diagnostic information but demonstrated duodenal ulcers in 2 and gastric ulcer in one of 5 patients not subjected to prior endoscopy Normal radiological findings were reported in the remaining 2 of these 5 cases

In 24 cases neither endoscopy nor barium meal examination was done for the following reasons recent endoscopy or barium meal had shown potentially bleeding lesions in 8 cases acute surgery without prior diagnostic examination was done in 4 cases severe alcoholism or advanced associated disease contraindicated further studies in 5 and 4 cases respectively 2 patients were very old and debilitated and one patient had only minor bleeding after acute salicylate overdosage

Red bleeding per anum In 2 patients rectoscopy revealed haemorrhoids only In 3 cases mild proctocolitis was found In one case with recurrent rectal bleeding during menstruation coloscopy showed a small area of petechiae in the sigmoid colon Biopsies did not reveal any signs of endometriosis In the last case a barium enema examination showed a large polyp in the sigmoid colon By coloscopy it was located to 30 cm from the anus and was shown to be bleeding diffusely Biopsies revealed no signs of malignancy

Therapeutic efforts

Haematemesis and/or melaena The results of treatment of the 91 patients with haematemesis and/or melaena are shown in Table IV The term cured implies that the bleeding was stopped and the resulting anaemia corrected Altogether 95 6% of these patients were thus cured from their acute bleeding episode and the mortality rate was 4 4%

Seven patients were operated on acutely within 6 days of admission The mean Hb level at the time of operation in these cases was 7 5 g/100 ml The remaining 4 cases were operated on 10 11 12 and 27 days after admission respectively

The operated patients 8 males and 3 females were 51–78 years old (mean 63) A bleeding ulcer was found in the duodenum in 7 cases in the stomach in one case and in the gastrojejunal stoma in one One patient had a diffuse bleeding from the mucosa of a hiatus hernia and one had liver cir

Table II *Diagnostic results of early endoscopy of the distal oesophagus stomach and duodenum in 62 patients with haematemesis and/or melaena*

Several patients had more than one type of lesion

	No of pats
No bleeding or potentially bleeding lesion found	12
Diffuse bleeding from the mucosa	5
Single or multiple erosions	18
Single or multiple ulcers	31
Varices	1

Table III *Location of endoscopically diagnosed bleeding or potentially bleeding lesions in the upper gastrointestinal tract of 50 patients with positive endoscopic findings*

Several patients had lesions in more than one organ

	No of pats
Oesophagus	5
Stomach	32
Duodenum	19
Jejunum (operated patients)	2

rhosis with bleeding oesophageal varices Nine patients were operated on in our hospital and 2 were transported to and operated on in the nearest large hospital situated 70 km away The operations performed were partial gastrectomy with gastrojejunostomy in 5 cases partial gastrectomy with gastroduodenostomy in 2 cases local ulcer resection with vagotomy in one case proximal selective vagotomy in one explorative laparotomy plus application of a Sengstaken tube in one and correction of a hiatus hernia in one case

Two patients died postperatively A 78 year old man with a bleeding duodenal ulcer operated on acutely on the third hospital day developed postoperative respiratory insufficiency and was therefore transported to and treated in the postoperative unit of the nearest large hospital He died 8 days later in a pulmonary oedema The patient with advanced liver cirrhosis and bleeding oesophageal varices died 3 weeks after operation due to a massive haemorrhage

Two patients died without any attempt at surgical treatment of their haemorrhage A 67 year old man with LED who had been taking steroids for one year died in an acute cardiac arrhythmia a few days after the bleeding had stopped and when his Hb level was starting to normalize The other death occurred in a 81 year-old man with chronic renal insufficiency in whom endoscopy had revealed

Table IV *Results of treatment of 91 cases with haematemesis and/or melaena*

	Treated	Cured	Deaths
Medical treatment only	80	78	
Acute surgery	7	5	2
Elective surgery	4	4	–
Total	91	87	4

haemorrhagic gastritis He continued to bleed despite medical treatment but was considered too ill for surgery

Red bleeding per anum In all 7 cases the bleeding ceased spontaneously The bleeding polyp in the sigmoid colon in one of the patients was later successfully removed The patient with rectal bleeding associated in time with her menstruations has continued to have intermittent minor bleeding and is still the subject of further studies Possibly she has localized angiodysplasia in the sigmoid

DISCUSSION

The yearly admission rate for acute gastrointestinal haemorrhage was reported to be 144 per 100000 inhabitants in southern Sweden (3) and 92 per 100000 in north-east Scotland (4) Our corresponding figure in southern Dalecarlia was 182 per 100000 If the 7 patients in our series admitted for acute red bleeding per anum are excluded the yearly admission rate within the total population falls to 168 per 100000 During the year of our prospective study therefore acute gastrointestinal haemorrhage was a significant cause of hospitalization in our district accounting for 2 2% of the total hospital admissions

In the series of Johnston et al (4) 8 7% of the patients were aged 80 years or more and 68% were males In our series 12% were 80 years or more and 64% were males More than 50% of our patients were aged 60 years or more Our series thus included a very high proportion of elderly patients

Our methods of acute treatment differed from the conventional ones only in the following respects We did not use gastric aspiration as a routine measure except in cases with severe haematemesis We administered antacids from the very beginning to all patients with haematemesis and/or melaena We administered tranexamic acid for 6 days to all patients with moderate or severe bleeding

The routine use of an antifibrinolytic agent seems justified in acute gastrointestinal haemorrhage when one considers the following points Psychological stress increases the fibrinolytic capacity of blood (2) The duration of hospitalization for patients with severe epistaxis can be significantly decreased by the administration of tranexamic acid (6) Local tissue activators of plasminogen possibly exist at the bleeding sites in the gastrointestinal canal (8)

Our choice of early panendoscopy of the distal oesophagus stomach and duodenum as the initial diagnostic method in cases of haematemesis and/or melaena rested on the following reasoning A barium meal examination can only reveal potentially bleeding lesions whereas endoscopy can show the actual bleeding site Endoscopy can reveal discrete and diffuse mucosal lesions not detectable with radiology Only endoscopy can answer the question whether bleeding is continuing or not

The diagnostic findings of our 62 early panendoscopies are rather similar to those of Cotton et al (1) who reported ulcers in 51% erosions in 11% and no detectable lesion in 14% of 208 patients examined Our corresponding figures were ulcers in 50% erosions in 29% and no detectable lesion in 19% The disturbingly high figure for negative endoscopies remains a problem The longer the preendoscopic delay the greater the chances of minor mucosal lesions healing undetected In our series a front or oblique viewing instrument would obviously have eliminated the possibility of undetected lesions in the proximal portions of the oesophagus At the time of the study however our hospital had only one gastroduodenoscope a side viewing one

St John et al (7) found an unusually high incidence of 13 2% of the Mallory Weiss syndrome in 121 patients subjected to emergency endoscopy within 8 hours of admission It is probable that the longer delay before endoscopy may at least partly explain the total lack of such findings in our series

Mortality figures in different series of acute ...ointestinal haemorrhage are influenced by the ...hod of selecting the patients and by the population from which they are drawn Our study was a prospective one and included all patients admitted to our hospital because of verified acute gastrointestinal haemorrhage The population from which our patients were drawn lived in small towns and in farming districts Several heavy steel factories are situated within the district Our surprisingly low overall mortality rate of 4 1% can be raised to 5 2% by excluding from the series the 21 5% of the 98 patients who did not bleed to Hb values below 12 0 g/100 ml A mortality rate of 5 2% is still very low however Palmer (5) reported a mortality rate of 7 9% in 1400 patients and Johnston et al (4) one of 13 7% in 817 patients In comparison to these two series ours is quite small An important contributing factor to our favourable results was the comparatively low percentage of patients with actual clinical signs of moderate or severe hypovolaemic shock Although almost half of the patients bled to Hb values below 8 9 g/100 ml only 11 showed clinical signs of severe arterial bleeding In the series of Johnston et al about ¼ of all patients showed a fall in Hb level to below 7 2 g/100 ml or signs of hypovolaemic shock

It is quite possible on the other hand that our way of handling and treating these patients did in fact substantially contribute to the very low overall mortality rate This seems even more likely when one considers the unusually high percentage of elderly patients in our series

It would seem therefore that the following factors contributed to our good results 1) Close observation of the patients in one ward under standardized conditions by a small number of doctors nurses and attendants responsible for their management and especially alert to signs of early insufficient peripheral circulation 2) Early administration of antacids and tranexamic acid 3) Early panendoscopy in cases with haematemesis and/or melaena

It is possible that one of the two postoperative deaths could have been avoided if our hospital had had a better postoperative care unit thereby eliminating the need for a long journey to the nearest large hospital

On the basis of this study it would seem that with modern diagnosis and treatment physicians and surgeons working in close co operation acute gastrointestinal haemorrhage can be successfully handled in a small district hospital

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Studies on Cerebrovascular Strokes

II Clinical Findings and Short term prognosis in a Stroke Material

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ABSTRACT This paper reports the second part of an investigation of first time cerebrovascular strokes in people under 70 years of age The clinical data of 344 patients, together with the short term outcome of the disease are presented The immediate (one month) overall mortality was 38% The corresponding percentage for cerebral haemorrhage was 86 for cerebral infarction 20 and for cerebral embolism 28 Of the surviving patients 111 had to be transferred to some form of institution at discharge after the acute phase 103 were able to return to their homes The influence of various factors upon the immediate prognosis is discussed Of the clinical findings the level of consciousness and a calculated score based on the neurological symptoms on admission proved to have the highest predictive value Using this score it was possible to predict the outcome in about 85% Single factors very highly associated with a poor prognosis were the co-existence of cardiac disease and renal insufficiency There was a notably high prevalence of hypercalcaemia

A study on the epidemiology of cerebrovascular stroke in persons below 70 years of age was presented in a previous paper (6) The study was based on a 5 year series comprising all patients with first time stroke in the county of Uppsala

The present paper reports the clinical findings on admission to hospital and the immediate outcome of the disease A further aim is to discuss factors associated with the prognosis and the possibilities of predicting the outcome at an early stage

MATERIAL AND METHODS

The selection of patients has been described in detail earlier (6) The material consisted of 91 patients with cerebral haemorrhage 225 with cerebral infarction and 28 with cerebral embolism The immediate outcome refers to the situation up to one month after the stroke Information was gathered from the hospital records concerning the history clinical status on admission and during hospitalization and all special examinations The level of consciousness neurological defects cardiac status and BP on admission were noted As most patients had had continuous BP measurements for at least the first week special care was taken to record the consecutive pressure values ECG recordings were obtained in most cases with a 12-channel direct ink writer and were evaluated by two physicians independently and primarily classified into four groups normal borderline normal borderline pathological and pathological according to the standard criteria set by the Department of Clinical Physiology at the hospital In the following the first two groups will be designated *normal* and the remaining two *pathological*

The laboratory data were obtained mainly by autoanalysers Thus information on electrolytes and other constituents in the blood were easily available The duration of hospitalization and the form of discharge (home or to an institution) were noted If the patient had died the autopsy record was sought The clinical status was assessed according to the score system suggested by Mathew et al (14) With a few modifications this system has been used throughout the present investigation (Table I)

Statistics

In order to describe the association between the outcome and various factors recorded on admission or in the history tabular descriptions are p esented (see Results)

As the various factors may be correlated and several of them may interact and together influence the prognosis and outcome it would seem appropriate to use some multivariate statistical method for the final analysis In this study we used the AID (Automatic Interaction Detector Computer Program) technique described in detail by Sonqvist and Morgan (19) The program is designed to determine which predictors and which combination of these reduce the variance in the dependent variable and to what degree this variance can be explained by the predictors A graphic presentation showing the predictive value of different factors and their interaction can further be obtained in the form of a predictor tree described in detail by Skoldenberg (18)

For analysis of the significance of various results the χ_2 test for comparison between two percentages was used Student's t test was used when applicable

Our choice of early panendoscopy of the distal oesophagus stomach and duodenum as the initial diagnostic method in cases of haematemesis and/or melaena rested on the following reasoning A barium meal examination can only reveal potentially bleeding lesions whereas endoscopy can show the actual bleeding site Endoscopy can reveal discrete and diffuse mucosal lesions not detectable with radiology Only endoscopy can answer the question whether bleeding is continuing or not

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Table III *Days of hospitalization*

	Men		Women		Total	
	Mean	Median	Mean	Median	Mean	Median
Cerebral haemorrhage (*n*=91)	6 3	2	6 2	2	6 1	2
Cerebral infarction (*n*=225)	16 3	18	20 0	18	18 2	18
Cerebral embolism (*n*=28)	18 2	19	17 3	14 5	16 6	16 5

Table IV *Number of patients with different neurological signs and distributions by level of consciousness and clinical score*

No of deaths within parentheses

	Cerebral haemorrhage	Cerebral infarction	Cerebral embolism
Neurological signs			
Right hemidisorder	26 (22)	81 (16)	16 (5)
Left hemidisorder	12 (8)	86 (5)	7 (0)
Combined right-left hemidisorder	50 (50)	23 (23)	1 (1)
Right monoplegia or paresis	2 (0)	15 (0)	1 (1)
Left monoplegia or paresis	0	9 (0)	1 (0)
Central facial palsy	42 (39)	88 (21)	9 (2)
Conjugate deviation	82 (77)	66 (42)	7 (5)
Babinski s sign	83 (76)	153 (40)	8 (6)
Level of consciousness			
Awake	5 (0)	96 (2)	15 (0)
Somnolent	10 (5)	86 (8)	9 (2)
Comatose semi comatose	76 (74)	43 (35)	4 (4)
Total	91 (79)	225 (45)	28 (6)
Clinical score			
0–14	63 (63)	29 (27)	3 (3)
15–24	19 (16)	16 (12)	5 (3)
25–	9 (0)	180 (6)	20 (0)
Total	91 (79)	225 (45)	28 (6)

Table V *Distribution of diastolic blood pressures on admission*

No of dead patients within parentheses

BP (mmHg)	Cerebral haemorrhage	Cerebral infarction	Cerebral embolism
0– 99	18 (11)	66 (13)	18 (3)
100–119	31 (30)	99 (17)	9 (2)
120–	42 (38)	60 (15)	1 (1)
Total	91 (79)	225 (45)	8 (6)

Table VI *Mean diastolic blood pressure (S D within parentheses) in surviving patients one week after the stroke compared with mean values for the same age groups in a health survey in the same county*

	Age group (y)		
	≤49	50–59	60–69
Men			
Hospital series	109 4 (26 17)	110 0 (17 22)	105 5 (16 65)
n	13	28	75
Health survey	87 7 (10 5)	93 1 (11 7)	94 2 (14 4)
n	266	164	154
Women			
Hospital series	100 3 (16 9)	105 3 (19 2)	106 7 (16 6)
n	12	35	86
Health survey	88 9 (10 6)	94 9 (11 3)	98 3 (12 1)
n	280	160	150

Table VII *Distribution of normal and pathological ECG among dead and surviving patients in the different diagnostic groups*

	ECG	Dead	Alive
Cerebral haemorrhage	Normal	5	9
	Pathological	54	0
	Missing	20	3
Cerebral infarction	Normal	2	68
	Pathological	38	58
	Missing	5	54
Cerebral embolism	Normal	1	0
	Pathological	5	19
	Missing	0	3
Total		130	214

Table I *Neurological evaluation of patients with acute stroke (modified after Mathew et al (14))*

Factor	Score
Mentation	
Level of consciousness	
Fully conscious	8
Somnolent	6
Precomatose	4
Comatose	0
Orientation	
Oriented×3	6
Oriented×2	4
Oriented×1	2
Disoriented	0
Speech	
Normal	23
Disconnected phrases	15
Expressive or impressive aphasia	10
Dumb	0
Cranial nerves	
No conjugate deviation	6
Conjugate deviation	0
Central facial function	
Intact	3
Palsy	0
Motor strength (each limb separately)	
Normal strength	5
Paresis	2
Paralysis	0
Performance disability status scale	
Normal	28
Moderate impairment	21
Considerable impairment	14
Severe impairment	7
No performance at all	0
Reflexes	
al	3
c	1
lexes	0
Sensation	
Normal	3
Mild sensory abnormality	2
Severe sensory abnormality	1
No response to pain	0
	100

RESULTS

Table II shows the distribution of the patients by age sex and diagnosis and the immediate outcome Of the 91 patients with cerebral haemorrhage 79 (86%) died in hospital The corresponding percentage for cerebral infarction was 20 and for embolism 28 A more detailed division showed that among the haemorrhages 72% of the deaths occurred within the first three days the corresponding figures for infarctions and embolisms were 60% and 33% respectively All except three of the patients who died were autopsied

The duration of hospitalization for the different diagnostic groups is shown in Table III As there was a considerable loss of patients during the first few days in hospital the median time was calculated as well as the mean

The essential clinical findings on admission are presented in Table IV The level of consciousness was considered of special importance for further prognostic analysis On admission 34% (=116/334) were fully awake mainly patients with embolism or infarction

As regards the neurological deficit there was a slight preponderance for right hemidisorders as in most other series (8 13) The clinical score was calculated as shown in Table I It will be seen from Table IV that low scores i e ≤24 were especially common among the haemorrhages

The distribution of the diastolic BP levels on admission is shown in Table V It is well known that an elevated BP can be an acute effect of the ictus and does not necessarily indicate hypertensive disease (1 8 15) For this reason the mean diastolic pressure after one week was calculated for surviving patients (Table VI) For comparison the table also gives mean values for each age group in a health survey in the same county (5) The level of the diastolic pressure in the stroke group is significantly higher than in the health survey series ($p<0.01$)

Table II *Distribution of the patients by age sex and diagnosis*

No of deaths within parentheses

	Age group (y)			
	≤49	50–59	60–69	Total
Cerebral haemorrhage				
Men	7 (5)	18 (17)	28 (24)	53 (46)
Women	6 (4)	10 (8)	22 (21)	38 (33)
Cerebral infarction				
Men	9 (1)	27 (9)	69 (15)	105 (25)
Women	12 (2)	25 (2)	83 (16)	120 (20)
Cerebral embolism				
Men	2 (0)	0	10 (2)	12 (2)
Women	0	5 (1)	11 (3)	16 (4)
Total	*36 (12)*	*85 (37)*	*223 (81)*	*344 (130)*

in Goteborg (8) Other Scandinavian authors (4 17) have also presented similar figures

The close agreement between these figures may seem somewhat surprising considering the incongruity of the materials The Goteborg material has an age distribution similar to that in our series but comprises cases of transitory ischaemic attacks (TIA) and recurrent strokes The influence of these two groups upon the immediate mortality is presumably small since the recurrences have a very high mortality while TIA of course have none The two Danish series include patients aged over 70 and should thus have had higher mortality figures However these studies date back to the 1950s and it can be assumed that at that time people died more often in their homes

The immediate cause of death may sometimes be difficult to ascertain In the majority of cases the cerebral damage is the sole and obvious cause of death The decision is less simple when there are concurrent signs of cardiac or pulmonary impairment To judge from our experience from the present series the mortality among patients with concomitant myocardial infarction or decompensation is very high suggesting that the cardiac affection might be a strong contributory factor if not in some cases the direct cause of death The role played by pneumonia or pulmonary congestion which are often found at autopsy is much more questionable In most cases it seems reasonable to look upon these phenomena as secondary or agonal as suggested by Geill (7)

The observed frequency of pathological ECGs is higher than in the overall population (5) Usually no ECG was recorded in patients who died within the first hours after admission Had these ECGs been included the number of pathological ECGs would certainly have been higher The exact significance of the pathological ECGs is somewhat obscure In many cases there were also other indications of cardiac affection It must be remembered that cerebrovascular lesions per se may give rise to ECG anomalies (3 20)

Table VII shows that especially for the cerebral haemorrhages a pathological ECG represents an unfavourable prognosis In cases of cerebral infarction a normal ECG predicts a favourable outcome An abnormal ECG is probably not only of importance for the outcome of a stroke In an epidemiological study Kannel (12) found that ECG evidence of coronary heart disease is associated with almost a five fold increase in risk of cerebral infarction

The number of patients with cardiac decompensation on admission was low compared with other series For example Robinson et al (15) reported a figure of 22% This difference can be explained partly by the lower age level of the present material It may also possibly be due to more extensive prophylactic treatment of cardiac failure and hypertension nowadays The presence of cardiac decompensation on admission especially in combination with hypertension and a pathological ECG carries a poor prognosis

Of the 8 patients with Ca, levels ≥5 3 mEq/l one highly suspected and one verified case of primary HPT were found The true figure may in fact have been somewhat higher as four patients were lost for further analysis Two of them were women in their sixties not taking thiazide and as far as can be found retrospectively not dehydrated which arouses suspicion of HPT In a recent survey of HPT in the same county Johansson et al (11) estimated the prevalence to be at least 1/1000 in ages over 40 years Thus the present figures are higher than expected This is in accordance with the suggestion of Bostrom and Alveryd (2) of a possible relationship between stroke and HPT As the present investigation only deals with completed strokes an even higher correlation might have been found if TIAs had also been included

Renal insufficiency is a poor prognostic sign for cerebral haemorrhage as well as for cerebral infarction The frequency of uraemia was fairly low (5 5%) compared with a series reported by Hood et al (9) They found a frequency of about 25% with a creatinine level above 2 0 mg/100 ml Another recent report has also given a low figure (10) Several factors may have contributed to the low frequency in our series Early tracing and more active treatment of both pyelonephritis and glomerulonephritis may be one During the last decade free purchase of phenacetin-containing analgesics has been abolished in Sweden presumably reducing the number of cases of non-obstructive pyelonephritis More intensive treatment of severe hypertension is probably another factor of importance

Various methods have been used to characterize the degree of disability One is to give a detailed description of the neurological deficit Naturally this gives precise information and the status can be followed from one point in time to another For

Table XI *Clinical features of patients unconscious on admission but surviving*

	Cerebral haemorrhage	Cerebral infarction
Diastolic BP		
≤99	2	4
100–119	0	4
120–	0	0
ECG normal	2	7
ECG pathological	*0*	*1*
Complicating disease	0	1 (diabetes)
No complicating disease	2	7
History of TIA	0	1
Hemiplegia	2	8
No history of previous hypertension	2	1
Inadequately treated hypertension	0	3
Adequately treated hypertension	0	4

comparisons between patients however it is less useful For instance it does not permit comparison of the disability of a hemiplegic with that of a patient with isolated ataxia or aphasia Some sort of index may be a better tool in interindividual comparison The system suggested by Mathew et al (14) and used in this study is easy to handle and seems to give a fairly proper basis at least for prediction of the immediate prognosis (Table IV)

It is of special interest to find out to what degree different factors are correlated to the immediate prognosis In this investigation the dependent variable used was discharged dead or alive from hospital and the independent variables were age sex ,iously known hypertension diabetes cardio ,erotic heart disease previous cerebral episodes (TIA) level of consciousness on admission diastolic BP Babinski s sign conjugated deviation of the eyes right hemidisorder left hemidisorder combined right and left hemidisorder central facial *paralysis and calculated clinical score*

As the patients with cerebral embolism formed a *very small group they will not be discussed separately* For both sexes there was a slight increase in mortality with increasing age in both the cerebral haemorrhage and cerebral infarction group The comparison based on sex yielded only one significant difference namely the mortality of men and women aged 50–59 years in the infarction group the male mortality being significantly higher than the female ($p<0\ 01$)

From the results it can be concluded that there is a correlation within the cerebral infarction group *between unfavourable prognosis and heredity* for cardiovascular disease previously known hypertension and cardiosclerotic heart disease No such correlation can be seen in the haemorrhage group and in neither of the groups did TIA or diabetes have any prognostic significance Within the groups of hypertension the form of treatment has no prognostic importance The significance of the diastolic BP level on admission is debatable as mentioned above It seems justifiable however to take this parameter into consideration as a prognostic predictor since it is influenced to some degree by the stroke process per se

The correlation between the neurological signs and the total score and immediate outcome of the *stroke is shown in Table IV In both diagnostic* groups the correlation between the level of consciousness and the immediate prognosis is very high Further analysis of the very few patients who were comatose or semicomatose on admission and survived shows that all except one regained full consciousness within two days It was of special interest to analyse these ten patients further As shown in *Table XI* they represent a selection of favourable factors namely low diastolic BP on admission normal ECG and a minimum of complicating factors The neurological deficits that correlated most highly to a poor prognosis are bilateral hemidisorder conjugate deviation Babinski's sign central facial paresis and low total score The correlation is specially high for the group of cerebral haemorrhages Where comparable the present findings of the prognostic criteria are in good accordance with earlier observations by several authors (4 13 17 21) all of whom particularly stress the importance of the level of consciousness

When an extensive number of correlations and differences is tested it must be remembered that *significant relationships may arise by chance alone* and without any biological background *Consequently the results of a statistical analysis of this* nature should be evaluated with caution and all significant relationships should be examined for biological explanations before being accepted

Multivariate analysis of prediction of mortality

From the findings it is clear that there are many factors of possible importance for the outcome There are considerable correlations between the

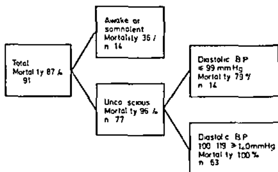


Fig 1 Predictor tree for the group with cerebral haemorrhages

explanatory factors Further it is highly possible that the factors may interact and influence the immediate outcome Thus the interpretation of a simple single correlation is not advisable and the situation calls for a multivariate analysis e g with the AID approach The main purpose of this analysis is to obtain a good prediction of the outcome and not an explanation of the biological process in itself

In the AID analysis the dependent variables were discharged dead or alive within one month The independent variables were age sex heredity for vascular disease previously known hypertension diabetes cardiac disease previous episodes of TIA diastolic BP on admission level of consciousness on admission focal neurological signs the score groups and year of admission Naturally the best result is obtained if the patients can be split into groups with 100% survival or 100% dead The AID specifies that the patients are not split into groups of less than ten

The predictor tree for the 91 cerebral haemorrhages is shown in Fig 1 The first split considers consciousness here 77 unconscious patients are placed in one group with a mortality amounting to 96% The remaining cases 14 patients awake or somnolent show a mortality of 36% The difference between the two percentages is highly significant The chosen split implies a stronger percentage difference than could have been obtained if the segmentation had been performed according to the other independent variables The split into score groups is however almost as important and could have been used instead without any noticeable changes in the significance It may be noted that the groups with the Babinski sign and eye deviation are too small to allow a split After this first split the group unconscious patients is further split into two groups according to the diastolic BP on admission It is noteworthy that all the 63 patients with a diastolic pressure ≥100 mmHg died The difference between the two groups with respect to mortality is significant Other factors do not give rise to the same degree of contrast in respect to mortality However the score groups could have given about the same significance and could have been used as a good substitute A further split was tried but did not give rise to any more groups According to the analysis one particular group with an extremely high mortality can be pointed out viz unconscious patients with an elevated diastolic BP on admission

A similar analysis with the same candidating factors was performed for the 225 patients with cerebral infarction Fig 2 shows that the main predictor is the score group A further split is made on combined right and left hemidisorder It may be noted that all patients with combined hemidisorders died and that the prognosis was very good for those with a score ≥25 with the possible exception of those with eye deviation A further analysis of the patients who died with a score over 25 shows that all but one had some form of complicating extracerebral condition such as acute myocardial infarction renal failure or cardiac decompensation

When the whole material is analysed by AID the different diagnoses are also taken into consideration as independent variables They do not however have any prognostic value per se The score has the

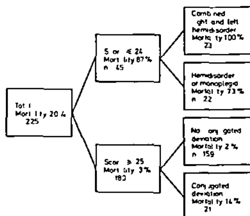


Fig 2 Predictor tree for the group with cerebral infarctions The split between the score groups is highly significant The following two splits are significant ($p < 0.05$) according to the method for significance analysis given by Skoldenberg (17)

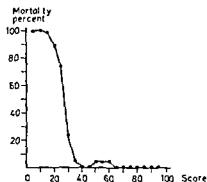


Fig 3 Correlation between the immediate mortality and the score

highest weight followed closely by consciousness and eye deviation Thus it can be concluded that the extent of brain damage and the resulting neurological deficit and not the diagnostic groups will predict the outcome To the AID analysis has been added a multiple regression analysis including the same factors Missing values of variables have been given a variable value between positive and negative (Due to the functional relation between the mortality and the score the multiple regression analysis was performed with transferred groups 0=score 0–19 1=score 20–24 2=score 25–29 and 3=score ≥30) Both the analyses give the score the greatest predictive value and the score dominates to such an extent that the presentation can be limited to Fig 3

It is obvious from Fig 3 that regardless of diagnosis the outcome good or unfavourable can be predicted by the score with a reasonable degree of certainty for most of the patients For an in ıediate group representing about 15% the ᴗy is less clear cut For patients with a score 15 the prognosis is 100% poor This group includes 95 patients Furthermore patients with a score ≥30 representing 200 patients have a good prognosis which can be predicted with a high degree of certainty The intermediate group with scores 15–29 comprises 49 patients representing 15% of the whole material for whom the prognosis is uncertain Even within this group however the outcome seems to be related to the score

To summarize the AID analysis has shown that for all the diagnostic groups there is close competition between the level of consciousness and the score calculated on the total neurological deficit to be the best predictor of the immediate mortality It therefore seems reasonable to consider whether the score system would not be still more indicative if higher relative importance were attributed to consciousness as well as to eye deviation and the Babinski sign

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Fine-needle Biopsy of the Liver Complicated with Bile Peritonitis

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ABSTRACT Fine needle biopsy has been performed on a healthy subject without any signs of liver disease, especially none of cholestasis During aspiration, bile appeared in the syringe, and laparotomy was necessary 24 hours later About 1 5 l bile was found in the abdominal cavity no lesions of the biliary system could be seen Treated with drainage the further course was uncomplicated

Fine needle biopsy has become a useful tool as a screening procedure in liver affections (3 8) especially in detection of malignancy (1 2 4 7) but also concerning metabolic disorders (6) It has been regarded as practically free from major complications Lundquist (5) reports one haemorrhage and no other serious complications in a series of 2611 fine needle biopsies

Bile peritonitis is not unknown in the conventional punch biopsy with the Menghini needle but to our knowledge no other case of this complication has been reported with the fine needle aspiration biopsy In our series of 150 fine needle biopsies the patients with bile peritonitis was the only one with complications

CASE REPORT

The patient a healthy male 190 cm high weight 90 kg was committed to an ambulant family screening for primary haemochromatosis including a fine needle biopsy of the liver He had had no previous major diseases and had felt healthy No abnormal findings were revealed at the general examination

The puncture was performed intercostally in the mid axillary line at the site of maximum dullness to percussion in expiration an lightness in inspiration the unanaesthetized patient holding his breath in deep expiration The needle connected to a 10 ml syrinee had an o d of 0 6 mm and was 10 cm long Aspiration started as the needle entered into the liver Bile appeared in the syringe and the needle was withdrawn After few seconds he felt a sharp pain in the upper right quadrant of the abdomen the abdominal wall became tender and he was admitted to the Surgical Department

Primary treatment was conservative but increasing pains and signs of ileus made a laparotomy necessary 24 hours after the puncture About 1 5 l bile was found in the abdominal cavity The corresponding wounds in the thorax wall and in the liver capsule localized low in the right lobe were found but no bile secretion was seen *Other perforations could not be found especially no lesion of the gallbladder* The laparotomy therefore was ended leaving two drains from near the gallbladder through the abdominal wall During the next 2-3 days spare bile secretion was noted and the drains were removed on the 5th and on the 6th day No other complications occurred

Blood samples taken before biopsy postoperatively and at controls 2 and 4 weeks postoperatively showed no signs of liver disease especially none of cholestasis The patient felt well at the controls

DISCUSSION

The perforation could have been intrahepatic—it is conceivable that the needle passed through the lower part of the right lobe and reached the gall bladder for technical reasons this area could not be inspected satisfactorily during the laparotomy The distance from the thorax wall to the gallbladder was not measured Liver cells were not found in the aspirated bile

The appearance of bile peritonitis after fine needle biopsy must be a rare condition but it should be kept in mind when judging the hazards of the method

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Premature Ventricular Beats with Narrow QRS Complexes

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ABSTRACT A case is presented with premature ventricular beats with narrow QRS complexes The arrhythmia is discussed on the basis of an ECG recording with 12 simultaneous ECG leads

Premature ventricular beats (PVB) with narrow QRS complexes appearing during sinus rhythm with bundle branch block is an interesting phenomenon Several cases of different mechanisms have been described in the literature (1 2 3 5 6 7) The present communication will report a case of a common mechanism studied by 12 simultaneous ECG leads

CASE REPORT

A man aged 79 who had previously had an acute myocardial infarction (AMI) and thereafter effort angina was admitted because of suspicion of another AMI which could not be confirmed later on

During 4 days in the CCU he constantly had the arrhythmia shown in Fig 1 The basic rhythm is sinus rhythm 93/min with a PR interval of 0 20 sec a QRS complex with a duration of 0 12 sec a mean frontal QRS vector of −44 and a rSr pattern in CR_2 thus a left anterior hemiblock and probably also an incomplete right bundle branch block (4) The sinus rhythm is interrupted by premature beats of varying configuration duration and coupling interval The QRS duration of these premature beats varies between 0 08 and 0 17 sec (Fig 2) The PR intervals change from 0 07 to 0 20 sec so that the shortest interval precedes the broadest QRS complexes and vice versa corresponding to varying R–R intervals

The variation of the coupling intervals (up to 0 15 sec) suggests a parasystolic ventricular rhythm The interectopic intervals corresponded well to even multiples of the shortest R–R interval The minimal quotient R–R /R–R was 0 75 the R–R interval being about 0 64 sec The covariation between the R–R intervals and the QRS configurations and durations also fits well in a parasystolic ventricular rhythm as fusion beats occur frequently in this rhythm

The most extreme QRS configuration is associated with a PR interval of only 0 07 sec and therefore probably represents a pure parasystolic activation This QRS configuration corresponds to a focus located distally in the anterior division of the left bundle branch The later in diastole this focus begins to activate the anterior part of the left ventricle the more of the posterior parts and of the right ventricle is simultaneously being activated by the sinus impulse and the more normal will the QRS configuration and duration be

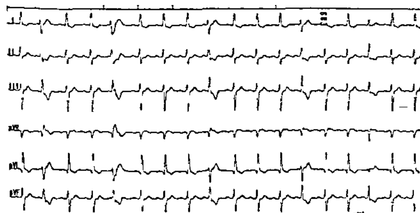


Fig 1 ECG recordings showing constant arrhythmia Paper speed 25 mm/sec

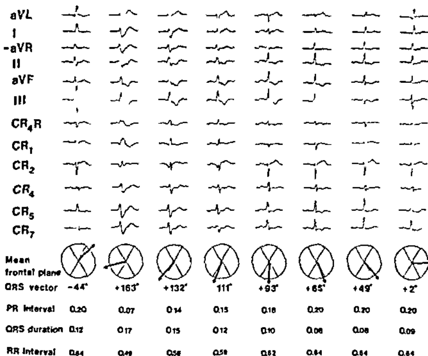


Fig 2 The first ECG strip is the sinus-conducted QRS complex The following strips are the VEB in order of successively increasing degree of fusion with the sinus beats All recordings at paper speed 50 mm/sec

DISCUSSION

The appearance of premature narrow QRS complexes in a sinus rhythm with fascicle/bundle branch block may be due to several mechanisms A premature junctional impulse may pass the injured bundle/fascicle without delay during the supernormal phase and simulate a PVB with narrow QRS complex *Bradycardia-dependent fascicle/bundle* branch block may disappear when cardiac cycles orten These two mechanisms could be excluded e present case as the premature narrow QRS es occur only very late in diastole The focus of PVBs with narrow QRS may be located proximally or distally in the blocked fascicle/bundle *With proximal location a slower antegrade con*duction in the injured fascicle/bundle must equal the longer pathways of the uninjured fascicle/bundle if the two ventricles shall be activated simultaneously (3) With distal location of the focus a narrow QRS can occur only by the fusion mechanism late in diastole

The correct identification of PVBs with narrow QRS complexes in a sinus rhythm with bundle branch block is not only of purely academic interest ECG signs of an acute or old myocardial infarction are most often obscured in the presence of left bundle branch block PVBs with narrow QRS complexes may then reveal the signs of an acute or old myocardial infarction

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EDITORIAL

Amyloid

Attempts at a biochemical characterization of amyloid have been made ever since Virchow some 150 years ago described this amorphous substance in many organs One of the great difficulties was the fact that it was impossible to bring amyloid into solution This problem was overcome in the most surprising way when Pras working in Ed Franklin s laboratory in New York discovered that the simplest of all solvents—namely distilled water—could be used to great advantage On addition of suitable amounts of electrolytes to the watery solution a precipitate of fibrils developed This was obviously an excellent material for further analysis

The fact that amyloid was chiefly known to occur together with two groups of clinical diseases A) chronic infections and B) disturbances of immunoglobulin formation has long been used as an argument in favour of the fact that parts of immunoglobulin molecules might be implied in the formation of this substance Osserman was able to demonstrate that patients with myeloma producing lambda chains were more prone to develop amyloid than those with kappa chains This was a strong argument that light chains may be part of the amyloid substance

The present number of this journal contains two papers treating an interesting type of familial amyloidosis that has recently been discovered in Northern Sweden One of the great biological problems is the preponderance of amyloid in certain organs in some families whereas quite different patterns of localization are present in others

A real breakthrough in amyloid study occurred when Glenner et al (7) published their investigations on the ultrastructural appearance of amyloid in tissues This was followed by very careful analysis It became clear that the problem of amyloid was more of a physico-chemical than of a biochemical nature Substances behaving like amyloid tinctorially e g with Congo red all consist of what is called a beta pleated sheet structure with regularly arranged always antiparallel polypeptide chains The typical fibrils may sometimes be parts of the light chain in an immunoglobulin molecule We have also reason to believe that parts of other polypeptide structures for instance calcitonin in medullary thyroid carcinoma and insulin in the pancreatic islets may constitute what has been described as amyloid in these locations Studies with the electron microscope have shown that the fibrils are of two types in many amyloid preparations The dominant amyloid fibril is soluble in distilled water and has been the subject of much study In so-called *secondary* "classical amyloidosis it seems as if a special protein that has been called SAA would be completely dominant in the plasma It is very interesting that this SAA protein may also be present in the serum in small quantities even in normal persons It increases very markedly with increasing age and may be found in 50 % of all persons above 70 whereas only 3 % of younger persons show this protein The molecular weight of serum protein SAA is very high whereas the fibrillary protein in amyloid has a molecular weight of ±9000 The serum protein may be found in increased amounts in a large number of conditions where amyloid may be suspected but also in a high percentage of normal pregnant women Experiments by Husby Natvig and their group indicate that a protein analogous to human SAA may be produced in mink after repeated endotoxin injections The animals then develop typical amyloidosis in liver and spleen

The biochemical situation still seems to be rather complicated but we may hope that metabolic studies in this condition like in so many other disease processes will give us the final solution For many decades it was thought that amyloid was a rather inert material that was irreversibly precipitated in the tissues Henning Waldenström was able to demonstrate by puncture of the liver that amyloid could be resorbed if the primary disease was cured This must mean that there is an equilibrium between precipitation and solution of amyloid material at least in chronic diseases

Patients with amyloid disease as the dominating symptom have been recognized much more often in later years when electrophoresis of serum protein has become more popular (8) In many such cases it is very difficult to decide if the patient has an atypical form of myeloma without bone destruction or "only amyloid In many patients we do not find any M-components or Bence Jones proteins but sometimes hypogammaglobulinemia is present In these patients it is probable that some disturbance of the plasmacellular system is present and some of these patients also have a high content of bone marrow plasma cells Parts of the variable half of light chains are probably present in the amyloid in such conditions as has been shown by Glenner and his group (7)

Perhaps the most enigmatic among the many types of diseases that are caused by or connected with deposition of amyloid are the *primary familial* The first to be described among these was the Portuguese amyloid that has an interesting geography as it is chiefly present in families of Portuguese descent also in Brazil (4) This type is also present in Japan and it has been discussed if this may have something to do with the Portuguese settlements in Japan around It is probable that this type with very marked affection of the peripheral nervous system may be the same as we seen it in some Swedish families described in this number of Acta Medica. There are however other families published with predilection of neuropathy in either the lower or the upper extremities It is possible that the latter group has chiefly the carpal tunnel syndrome as an

explanation of predilection for the upper extremities This group also has opacities in the vitreous body whereas a recently described type of hereditary amyloidosis in Fin land (9) has corneal opacities as one of the chief clinical symptoms The fact that amyloid in the cornea is pre cipitated along the nerves may be an indication that the substance is a product of nerve metabolism and is formed in loco Amyloid may be a type of fibrillosis developing *in many metabolic disturbances of polypeptide synthesis* It seems as if all these conditions were inherited as auto-somal dominant traits

Some Scandinavian reports from the last decade are of interest Danish authors observed a family with 5/12 sib-lings who probably had amyloid disease especially in the heart with early death form cardiac disease (6) The amy loid was located in the heart and the tongue but the peri pheral nerves also contained some amyloid that did not give any clinical symptom So far this type of disease seems to be unique In 1968 Swedish authors published the case histories from patients in a family with severe nephropathy (5) The earlier history was dominated by at tacks of abdominal pain and febrile episodes with increase in the ESR These attacks preceded the signs of renal dis-ease One of these patients was also described earlier as a case of possibly familial Mediterranean fever (FMF) I saw this patient many years ago in Uppsala and have later regarded him and his brother as an undoubted instance of FMF in a family of pure non mediterranean origin They died from renal amyloid As a matter of fact I have seen a completely similar case also from the North of Sweden but with no diseased family members

Goldfinger has recently published excellent results in the treatment of FMF with colchicine These results have been amply confirmed in Israel regarding the clinical symptoms but it is still too early to state if continued treatment with this drug will protect against amyloid At the recent meet ing on amyloid in Helsinki I pointed out the fact that so many types of amyloid occur in febrile conditions Is fever of importance?

A group of internists in Umeå has recently studied sev eral large families with this disease and have published their results in a series of papers in the Acta Medica Scandinavi ca (2 3) In these patients the neuropathy is the dominant ing even if diarrhea has been noted in many patients veral patients have had vitreous opacities One of the ies comes from Finland Uremia has been noted but amyloid in the kidney is quite inconstant and some have died without any renal amyloidosis whereas the peripher al nervous system is very heavily affected It seems as if these patients had a Portuguese type of hereditary amy loid

This family of Finnish descent does not seem to be related to a number of Finnish patients with an interesting type of disease pattern recently described by Meretoja (9) in a series of papers during the years 1969–73 The condi tion is inherited as a dominant trait with an equal sex ratio The patients live in some very strictly defined districts in Finland The clinical picture is dominated by cranial neuropathy especially the facial There are diffuse amy loid deposits also in the dura of the brain and of the spinal cord The dominating symptom is a so-called lattice cor *neal dystrophy and these patients were all originally de* tected by ophthalmologists The lattice is formed by amy loid deposits in the fine nerves of the cornea This is dif ferent from the vitreous opacities that also have been the cause of severe visual disturbance in other families The patterns are true to type

A number of other hereditary types are known from the literature One with hereditary cutaneous amyloidosis lichen amyloidosys is especially found in Malaysia An other with urticaria deafness and renal diseases occurs in England The amyloid in medullary thyroid carcinoma is not of the hereditary type and is obviously connected with the formation of calcitonin My guess is that amyloid represents a biochemically heterogenous group of condi tions that have nothing in common except the morpho-logic appearance As always biochemistry will give a clear picture of the underlying physiological mechanism

Jan G Waldenström

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The Nitroblue Tetrazolium (NBT) Test in Endemic Benign (Epidemic) Nephropathy

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ABSTRACT NBT test values in blood samples from 25 cases of endemic benign (epidemic) nephropathy (EBN) were high, i e more than 19 % NBT positive neutrophils, in 22 (88 %) of the patients intermediate, i e 13–19 %, in two (8 %) and normal in one patient (4 %), in eight patients (32 %) the NBT test values were 50 % or more The test values remained elevated, i e 13 % or more, for more than one month after the onset of illness in three of ten patients on whom serial tests were performed Among 18 patients with kidney diseases other than EBN and 16 with kidney transplant, high NBT test values, 20 and 22 % respectively, were found in two (5 9 %) intermediate values in two and normal test values in 30 patients (88 2 %) This paper is the first published report on NBT test values in cases of EBN The test was rated to be of diagnostic value in patients in whom EBN might be suspected, highly elevated test values (≥50 % NBT positive neutrophils) lending support to the diagnosis

Applying the Nitroblue tetrazolium (NBT) test introduced by Park et al in 1968 (15) neutrophilic granulocytes may be divided into NBT positive and NBT negative depending on whether or not they reduce NBT to nitroblue formazan

In patients with untreated bacterial fungal or parasitic infections the proportion of NBT positive neutrophils was found to be raised (7 11 15) whereas in patients with viral infections test values were normal The test was recommended for routine use in the differentiation of various kinds of infections (5 8) but in subsequent papers (2 9) the advantage of this practice has been questioned

Although the etiology of endemic benign (epidemic) nephropathy (EBN) remains undetermined the symptoms of the disease are compatible with those of an acute infection The diagnosis remains a clinical one as long as no (laboratory) tests of a discriminating character have been found associated with the condition The findings of elevated NBT test values in cases of EBN are therefore of interest

MATERIAL AND METHODS

Twenty five patients with EBN 17 males and 8 females aged 17–58 years (mean 36) 18 with kidney diseases other than EBN and 16 with kidney transplants were studied The cases of EBN were diagnosed using common clinical criteria (13) sudden onset of illness with elevated body temperature ache or pain in the back and in the abdomen and gastrointestinal symptoms in a majority of the patients a period of oliguria lasting a few days was followed by polyuria for about a week Laboratory findings on admission invariably included proteinuria and elevated non-protein serum creatinine None of the patients had a bacterial urinary infection at the time of investigation ten were treated with antimicrobial drugs (penicillin sulfonamides or nitrofurantoin) The disease was self limiting and all the patients recovered within less than 10 weeks A detailed account of the disease is given in papers on epidemic nephropathy (10 12 14 17)

The NBT tests were performed on venous blood samples employing a strictly standardized technique (1) Test values of less than 13 % NBT positive neutrophilic granulocytes were considered to be normal (4) values above that were rated as elevated 13–19 % being considered intermediate and more than 19 % high

To check the ability of the neutrophils to reduce NBT blood samples from all patients were incubated for 10 min with 10 μg endotoxin (E coli 0 111 lipopolysaccharide Difco Laboratories Detroit Mich USA) whereafter the NBT test was repeated

RESULTS

The NBT test values were high (Fig 1) in 22 (88 %) and intermediate in two (8 %) of the patients with EBN A normal test value was found in only one

patient (4%) when stimulated with endotoxin 82% of her neutrophils were NBT positive indicating that they were capable of reducing NBT

There was no difference in the distribution of NBT test values between patients treated and those not treated with antimicrobial drugs nor did the mean of the maximum leukocyte count and of serum creatinine level differ between these groups (Wilcoxon s t test for non parametric observa tions)

In kidney diseases with an acute onset other than EBN (Table I) high NBT test values 22 and 20% respectively were found in one patient of two with acute tubular necrosis and in one of three with interstitial nephritis intermediate test values were obtained in one patient with proliferative glomerulonephritis and in one with kidney trans plant In the remaining 15 patients with a kidney dis

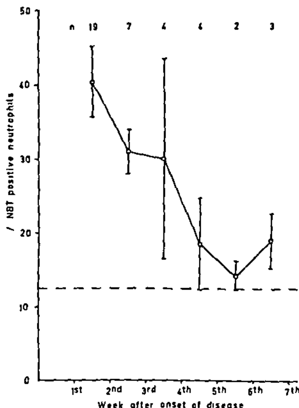


Fig 2 Mean values±S E M of weekly determinations of NBT test values in 25 cases of EBN =upper limit for normal test values

ease other than EBN and in 15 with kidney trans plant (88 2%) NBT test values were normal

Serial tests were performed in 10 patients with EBN and high NBT test values (Fig 1) In four patients the NBT test values were normal after 4–5 weeks and in two after 6 and 12 weeks respective ly In four patients the NBT test values were still elevated after 3–7 weeks

Fig 2 presents the mean values of 40 NBT tests in 25 cases of EBN excluding one normal value obtained on the 85th day after the onset of disease The test values remained high up to the fifth week and were still intermediate seven weeks after the patient had contracted the disease

Fig 1 Initial NBT test values in 25 cases of EBN and results of serial deter minations =upper limit for normal test values

DISCUSSION

The proportion of patients with high NBT test values was greater in EBN than in infectious diseases of known etiology and previously investigated (2). Very high test values, i.e. 50% NBT positive neutrophils or more, were found in eight of the patients (31.3%); in conditions with an infectious etiology test values of such a magnitude were obtained only occasionally, e.g. in cases of acute osteomyelitis (unpublished observations).

The high NBT test values associated with EBN are interesting, since they are most commonly found during the acute phase of the disease. Uraemia does not give rise to high NBT test values if the patients are free from infection (16). The etiology of the disease is undertermined but several authors consider it viral (10, 12, 14). High NBT test values are, however, usually not found in viral infections (5, 8) and in another study (2) elevated test values were found in only 14% of blood samples from patients with viroses.

On the other hand, NBT test values are often high in mycoplasmal infections (2, 6). Assuming that EBN is caused by an as yet unidentified mycoplasmal species, this might explain the high NBT test values found in patients with this disease.

Although the mechanisms underlying the NBT test are only partially known, this study indicates that the test may be rated as a valuable aid in the diagnosis of EBN, normal test values speaking against the disease and very high test values lending support to the diagnosis. As the NBT test values in some cases remained elevated for several weeks after the onset of disease and the subsidence of azotaemia, the test might also be of use as a diagnostic aid even if a case of suspected EBN is not seen until late in the course of the disease.

Table I. *Distribution of NBT test values in cases of kidney disease other than EBN and in patients with kidney transplant*

Clinical diagnosis	No. of cases with NBT test value (%) of		
	≤12	13–19	>19
Glomerulonephritis, acute and proliferative	3	1	
Acute tubular necrosis	1		1
Polycystic kidneys, interstitial nephritis, chronic pyelonephritis	7		1
Collagenic disorders with renal involvement	4		
Kidney transplant	15	1	
Total	30	2	2

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Bacteriological and Clinical Evaluation of Different Dialysate Delivery Systems

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ABSTRACT In the period 1964–74 four different dialysate delivery systems have been used in our department 1) Central mixing of dialysate using tap water and a dialysate delivery line with "dead ends" resulting in stagnant dialysate 2) Central mixing of dialysate with cold distilled water, otherwise equal to system 1 3) Local mixing of dialysate with cold distilled water delivered through a line with "dead ends" resulting in stagnant water 4) Local mixing of dialysate with distilled water, cooled to 25 C just prior to use, reduced "dead ends" and monitored constant overflow to drain through the water supply line The bacterial contamination of the four systems was examined and related to the clinical occurrence of pyrogenic and other reactions An improvement was noted with the change from central to local mixing of dialysate (system 3) but complete sterility and virtual freedom from clinical reactions were first obtained in system 4 It is concluded that the use of sterile or near sterile dialysate is recommendable

Although it is usually accepted that the dialysis membrane is relatively impermeable to bacteria (and perhaps also to vira) pyrogenic reactions are well known symptoms during dialysis treatment with a heavily contaminated dialysate (14) Pyrogenic reactions are mostly due to the passage of bacterial toxins through the dialysis membrane although direct passage of bacteria can occur (9 11 12 13 15 16)

It has been demonstrated that antibodies to dialysable bacterial endotoxins are present in the serum of many dialysis patients (9 11) Further it has been found that a bacterial count in the dialysate exceeding 10^6 col /ml is associated with an *increasing frequency of severe pyrogenic reactions* (12) The reported frequency of all types of pyrogenic reactions (mild and severe) varies in different materials Excluding febrile reactions associated with blood transfusions demonstrable infections and drugs Robinson and Rosen *(14)* found that about 10% of dialytic treatments result in elevation of body temperature often accompanied by symptoms of varying severity (e g vomiting abdominal or back pain and hypotension)

Since 1964 four different types of dialysate delivery systems have consecutively been used in our department systems which were designed to be of increasing value in the prevention of bacterial contamination of the dialysate It is the purpose of the present paper to report on the degree of contamination and its correlation to the clinical symptoms in these four systems

DESCRIPTION OF THE FOUR DIALYSATE DELIVERY SYSTEMS

System 1 (Fig 1) uses tap water batch mixing of dialysate subsequently heated to 25°C dialysate delivery line with stagnating dialysate and non-heat sterilizable monitors *Water* was of cold deep subsoil quality (8–11°C) *Mixing* of tap water with pyrogen-tested dry salts or with sterile salt concentrates was carried out in a stainless steel tank containing 1000 l *Dialysate delivery line* was made of pyrex glass with teflon fittings It had "dead ends" not only at the terminal point but also at each individual tap site The dialysate was run from the mixing tank through the line into local tanks each containing about 150 l (not shown in Fig 1) *Monitors* contained a heating unit to increase dialysate temperature to

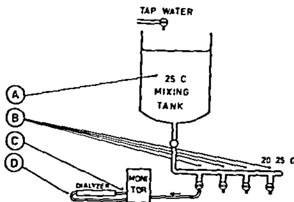


Fig 1 Diagram of system 1 using tap water and batch mixing

38°C and an effluent centrifugal pump The entire dialysate delivery system and the monitors were cleaned and sterilized by flushing with hot tap water after each use and filled with 2% formalin solution. Prior to use the formalin was washed out with hot tap water

System 2 (Fig 2) uses 25°C distilled water from a distillation plant which has been described in an earlier paper (3) but is otherwise identical to system 1

System 3 (Fig 3) uses distilled water delivered at 25°C from a storage tank with continuous overflow The delivery line for distilled water is a single pipe of stainless steel with stagnant water in the whole length when not in use Local mixing of dialysate is performed in monitors which are sterilizable by heat and chemicals. This equipment has earlier been described in detail (4 5) Cleaning and sterilization of the delivery line for distilled water as in systems 1 and 2

System 4 (Fig 4) uses hot distilled sterile water cooled just before use to 25°C The water delivery line has reduced dead ends at the tap sites and has a continuous throughflow of water regardless whether the dialysis stations are in use or not (3) Local mixing of distilled water and concentrate in sterilizable monitors as in system 3

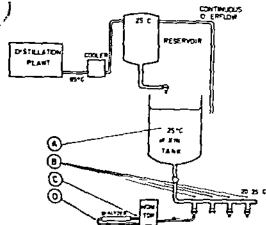


Fig 2 Diagram of system 2 using distilled water and batch mixing

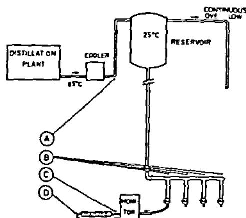


Fig 3 Diagram of system 3 using distilled water via storage tank and local mixing

BACTERIOLOGICAL METHODS

Cultures were taken from four comparable sites (A B C D) in each system as indicated in Figs 1–4 One or two portions of 500 ml fluid was collected aseptically in sterile bottles The sample was drawn through a sterile microporous filter (Millipore* 0 45 μ) The filter was then transferred aseptically to the surface of blood yeast agar substrate in a Petri dish and incubated at 35°C for 24 and 48 hours The number of colonies was counted with a magnifying-glass Identification of the colonies was made by conventional technique

REGISTRATION OF SYMPTOMS

Pyrogenic reactions were defined as an increase in temperature of at least 0 6°C and a peak temperature of at least 37 7°C Fever due to known active infections to transfusions and to drugs was disregarded Pyrogenic reactions were commonly associated with different symptoms of varying intensity and were graded accord

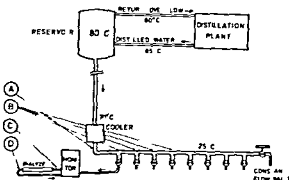


Fig 4 Diagram of system 4 using hot distilled water cooled prior to use and local mixing

Table I *Pattern of bacterial counts in systems 1–4*

Culture sites	No of samples	Bacterial counts in sample (col /l) 0–50 (%)	51–500 (%)	>500 (%)
System 1				
A	160	100	0	0
B	397	87	4	9
C	393	73	6	21
D	428	76	7	17
System 2				
A	131	92	2	6
B	355	81	5	14
C	227	70	1	29
D	501	69	7	24
System 3				
A	160	94	6	0
B	353	47	24	29
C	351	55	24	21
D	346	58	23	19
System 4				
A	42	100	0	0
B	83	100	0	0
C	133	100	0	0
D	133	94	6	0

ingly Grade 1) No associated symptoms Grade 2) Slight symptoms (i e headache and/or vomiting and/or chills) Grade 3) Severe symptoms (i e BP drop and/or recurrent vomiting and/or pain in lower back or abdomen and/or pronounced malaise)

Other reactions Symptoms of grades 1–3 according to the definitions above could also occur in the absence of fever Disregarding dysequilibrium syndrome too rapid ultrafiltration and other conditions not associated with the dialytic procedure such symptoms may be due to endotoxins as recently shown by Gazenfeldt-Gazit and Eliahou (9) In the present material they were graded as follows Slight symptoms severe headache episode of vomiting transient abdominal pain transient BP drop Severe symptoms repeated vomiting low back or abdominal pain marked BP drop

RESULTS

Table I illustrates the percentage of consecutive samples which were found contaminated at the points A B C and D in the four different systems shown in Figs 1–4 It appears that the degree of contamination increases from point A to D without any significant difference between systems 1–3 whereas system 4 is sterile for all practical purposes Repeated testing of system 4 at irregular intervals over an extended period confirms this observation

It should be emphasized in this context that systems 1–3 remained infected despite the extensive daily cleaning and sterilization procedures mentioned in the description of the four dialysate delivery systems In contradistinction system 4 remained sterile over an observation period of 4 years without any cleaning and sterilization of the water delivery line

Table II shows the clinical symptoms graded

Table II *Frequency of fever in the different systems and relation to accompanying symptoms*

System	Pyrogenic reactions (%) No symptoms	Slight symptoms	Severe symptoms	Total	Other reactions (%) No symptoms	Slight symptoms	Severe symptoms
1	2 2	5 7	4 5	12 4	59 6	17 3	10 6
2	4 2	2 2	0 8	7 8	55 4	33 3	4 1
3	1 6	2 2	1 6	5 8	79 6	9 7	5 3
4	1 5	0 3	0 0	1 8	95 6	2 5	0 1

Table III *Bacterial species related to symptoms*

	No of samples	Symptoms (%) No	Slight	Severe	Comments
Ps aeruginosa	194	32	63	5	Mainly headache and fever
Ps stutzeri	115	12	51	37	BP instability vomiting malaise
Enterobact cloacae	30	14	71	15	*Headache and BP instability*
Klebsiella oxytoca	24	0	42	58	Headache and BP instability
Bacterium anitratum	8	0	37	63	BP instability

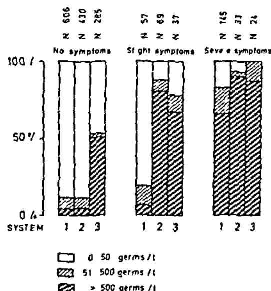


Fig 5 Correlation between symptoms and bacterial contamination of the dialysate in systems 1 2 and 3

according to their severity Although the contamination of systems 1–3 is of the same order of magnitude it appears that system 3 (with local mixing of water and concentrate) is better than systems 1 and 2 with central mixing However only system 4 shows a very low incidence of pyrogenic and other reactions

Fig 5 shows the relation between severity of symptoms (irrespective of the presence of fever) in relation to the degree of bacterial contamination There seems to be a clear-cut correlation between the severity of symptoms and the degree of contamination in systems 1 2 and 3

The relation between the species of bacteria and the clinical symptoms has been evaluated In systems 1 and 2 more than 70% of the significantly contaminated samples (>500 col /l) contained two or more species which makes it difficult to evaluate the reactivity to any specific bacteria Analysis of the material does however indicate that a mixed contamination gives rise to a higher frequency and severity of reactions

In order to evaluate possible differences in the clinical reactivity to specific bacteria 371 dialysate samples which were contaminated with only one fully identified bacterial species were considered The results are shown in Table III

Ps aeruginosa seems quite harmless from a clinical point of view which is fortunate as this species is the most commonly found and tends to dominate other bacteria once it is established in the pipe system The situation becomes dangerous once a change in the species occurs (2) Especially Klebsiella oxytoca and B anitratum appear to give rise to frequent reactions The main clinical finding in connection with these bacterial contaminants is pronounced instability of BP and circulatory failure

Despite almost sterile conditions a low frequency of fever is seen in system 4 obviously of non bacterial origin The results from 7 out of 27 patients in a prospective study over 3 months is shown in Table IV The 7 patients all have in common pronounced symptoms of anemia necessitating regular transfusions Only one of the remaining 20 patients received regular transfusions (10/year)

DISCUSSION

Despite the introduction of sterile disposable dialysers clinical reactions caused by bacterial contamination of the dialysate are still in evidence The frequency has been reported to be about 10% (14) and a good correlation has been found between the degree of contamination and the severity of the reactions (6 7 9 10 12)

The latter finding is supported by the present study as shown in Fig 5 The present study also permits an evaluation of the correlation between the species of contaminating bacteria and clinical reactions The results shown in Table III demon

Table IV *Pyrogenic reactions during 752 hemodialyses*

	Pat no							Total	
	1	2	3	4	5	6*	7	n	%
Fever during dialysis	2	6	3	2	2	1	1	17	2 3
No symptoms	2	5	3	2	0	1	1	14	1 9
Slight symptoms	0	1	0	0	2	0	0	3	0 4
Severe symptoms	0	0	0	0	0	0	0	0	
Approx trans fusions/y	8	24	12	8	12	18	4		
Cultures taken	2	6	3	2	2	1	1	17	
Growth in water	0	0	0	0	0	0	0	0	
Growth in system	1	0	0	0	(1)	0	0	2	
Growth in blood	0	0	0	0	0	0	0	0	

* Treated topically in shunt with thrombolytic enzymes (Brinase®)

strate that contamination of the dialysate with Klebsiella oxytoca and Bacterium anitratum is more hazardous than the three other commonly occurring contaminants in our systems

Off hand one might expect that local mixing of the dialysate and the use of fully sterilizable monitors might eliminate the problem A reduction in the frequency and in the severity of reactions was in fact observed when these precautions were introduced (cf system 3 to systems 1 and 2 in Table III) It is quite clear however that the precautions are not sufficient per se

A dramatic reduction in the number of clinical reactions was first observed when the entire system was kept sterile throughout (system 4 Table III) The very few reactions still occurring in this situation must apparently be explained by factors unrelated to the quality of the dialysate

System 4 has previously been described in detail (3) In brief it operates with freshly produced sterile (and distilled) water cooled shortly before use and delivered through a pipeline with continous overflow avoiding all possibilities for stagnation The water is mixed locally with concentrate in monitors which are fully sterilizable (by heat and chemicals) between each use The expense of this system has previously been calculated to be 0 032 D kr /l water (3) However since the pipeline remains sterile automatically personnel hours for cleaning and sterilization of the pipeline are saved

In conclusion we find that the use of dialysate with the lowest possible degree of contamination is highly recommendable In a center this may be achieved by introducing a system which has all—or at least most of—the merits of our system 4 In the home such a system is hardly economically acceptable but it is recommendable to take all precautions to prevent contamination of those compounds which are most liable to permit bacterial multiplication

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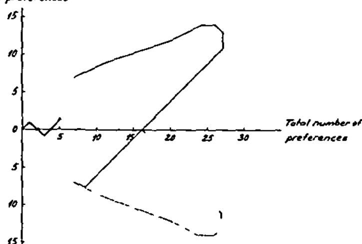


Fig 1 Sequential analysis diagram with result line drawn in —= limits for a one sided test - - - = alteration for extension to a two sided test

through them TD with constant data for the tube was determined by thermoluminiscence dosimetry

Blood flow was measured either with an electromagnetic flowmeter (Nycotron) or by determination of air bubble speed using an empirical formula, flow= 4 25×length of tubing (cm)/ passage time (sec) In this study TD was fixed at 400 rad CD was calculated from TD period of treatment and blood volume (CD=TD (rad)×blood flow (ml)×60×period of treatment (h)/ blood volume (ml)=rad) CDs of approximately 50 000 rad were given both before and as soon as possible after RAT Patients treated before and after RAT received CDs of 47051±10991 rad (mean ±1 S D) before and 45671±10249 rad after RAT For all patients treated before RAT the CD was 45940±11407 rad Blood volumes for men were calculated from the formula 2937+26 87× body weight (kg) and for women 1124+42 6×body weight (kg) Uncertainty in the determination of blood flow and volume is discussed in an earlier publication (5)

ECIB and RAT

A controlled clinical investigation was carried out Patients were allocated randomly to a treated group (+ECIB) and a control group (0-ECIB)

The primary purpose of the investigation was to determine whether ECIB could produce a significant change in the number of rejections in the treated group ECIB was given according to predetermined conditions (fixed-dose trial) both before and after RAT and the results were compared with a control group which as far as possible differed from the treated group only in ECIB

Sequential analysis (skew restricted sequential design) was chosen as the statistical method for this part of the investigation This method is patient-saving and the fastest method of obtaining a significant result A one sided test was used because it was assumed that ECIB would not worsen the results of transplantation

In the construction of the sequence diagram (Fig 1) errors of types 1 and 2 were given the values $2\alpha=\beta=0$ 05 and $\theta=0$ 85 was used as clinical significance level Further details of the principle of this method can be found in the publications by Bross (6) and Armitage (2) By the method chosen a significant result of the selected problem is ensured within a maximum of 27 preferences Using this method a result is ensured for one variable only and the analysis is complete when this result has been obtained Other tests of significance must be employed to determine whether there are significant differences in the remaining variables

Because the progress of the sequential analysis was slow the material in the controlled trial became so large

Table I *Reasons for exclusions from sequential analysis*

	+ECIB	0-ECIB	p[b]
Total no of pats	55	46	
Dead before RAT	14[a]	6[a]	0 06
Not transplanted before Dec 31 1974	16	11	
Unfinished post RAT ECIB	4[a]		
Graftectomized or dead without rejection before 60th day after RAT	4[a]	5[a]	
Transplanted in other centre	0	2[a]	
Total exclusions	38	24	0 04
Input material in sequential analysis	17	22	

[a] Blindly replaced with new patients according to the premises of the analysis 22 +ECIB and 13 0-ECIB patients have been replaced in this way

[b] Fisher s exact test

Table II *Distribution by sex age and renal diseases in the treated and control groups*
Glom = chronic glomerulonephritis Pyel = chronic pyelonephritis Cyst = renal cystic disease Diab = diabetes NSCL = nephrosclerosis

	No of pats	♂	♀	Age (y)	Glom	Pyel	Cyst	Diab	NSCL	Other
+ECIB	55	27	28	44 7±10 6 (22–66)	17	19	5	8	3	3
0-ECIB	46	18	28	44 1±12 0 (13–64)	14	21	4	4	3	0
p		0 1	0 08	–	0 17	0 09	0 27	0 17	0 31	0 16
p[a]		–		n s	–	–	–	–	–	–

Fisher s exact test [a] *Mann Whitney probability test n s = not significant* *Mean±1 S D range within* parentheses

that it was possible to study the influence of ECIB on patient survival both in relation to group allocation and in relation to RAT and the time and number of rejections and graftectomies These relationships were evaluated statistically using Mann Whitney probability tests Fisher's exact probability tests survival curves by the decrement method and comparison of decrement curves using χ^2 tests

Randomization

All patients undergoing hemodialysis in preparation for kidney transplantation at a later date were included in the material with the exception of previously transplanted patients and patients previously treated with other types of ECIB (250 kV X rays or ^{90}Sr ^{90}Y source) or endolymphatic irradiation (^{198}Au or ^{32}P) In the observation period of 3½ years 101 patients were allocated in this way and 2 3 and 3 patients respectively were excluded from the material

The allocation of patients to +ECIB and 0–ECIB groups was made using random numbers Patients were treated with a TD of 400 rad in consecutive dialyses up to a CD of 50 000 rad As soon as possible after RAT the patients were again treated with 50 000 rad Patients in both groups were observed for rejection during 60 days following RAT This period was chosen partly because in practice it is possible to give the planned ECIB within this period and partly because experience shows that this period is especially critical with respect to the risk of rejection episodes Substantial immunosuppressive properties could thus be attributed to ECIB provided the treatment could reduce the frequency of rejection in this period

Sixty days after RAT the patients were paired for sequential analysis The first +ECIB patient was compared with the first 0–ECIB patient If both patients in a pair either had or had not rejected the graft (tied pairs) they were not included in the analysis If the ECIB treated patient in contrast to the control patient had not rejected the graft the pair was given a value +1 and in the opposite case −1 When rejection had been diagnosed this part of the investigation was complete for the patient in question because the further treatment and development of rejection has no relevance in the sequential analysis The diagnosis of rejection was made according to the department s usual criteria (biopsy decrease in clearance decreased diuresis etc) after exclusion of other possible explanations for reduced graft function

The plan for the investigation included a number of reasons for exclusion which are listed in Table I together with a number of other grounds for alteration of the primary rejection diagnosis rejection diagnosed within seven days after the end of the 60 days delayed start of ECIB after allocation transplantation of a graft which never functions together with possibilities for repetition of ECIB if lymphocyte count rose to pre ECIB values before RAT As none of these possibilities were realized a more detailed description of them is not included here All excluded patients were replaced blindly by new patients in accordance with the principle of the analysis (Table I)

Additional immunosuppressive treatment with pred

Table III *Influence of ECIB on the results after renal allotransplantation*

	+ECIB	0-ECIB	*p*
RAT	25	28	
Rejection before 60th day	9	13	0 17
All rejections before graftectomy death or Dec 31 1974	13	18	0 15
Two or more rejections (same period)	8	3	0 05
Graftectomy before death or Dec 31 1974	5	12	0 05
Deaths			
After RAT (same period)	13	7	0 03
Total (same period)	27	12	0 01

Fisher s exact test

Table IV *ECIB and renal allotransplantation —match degrees*

	No of pats	RAT	Mismatch			
			0	1	2	3
+ECIB	55	25	2	7	14	2
0-ECIB	46	28	3	10	15	0
P^*		0 05	0 34	0 18	0 21	0 22

* Fisher s exact test

nisolone and azathioprine was the same in the two groups Methyl prednisolone was given during transplantation in a dose of 1 g followed by 50 mg/day for five days and 1 mg/kg/day until day 30 The daily dose was then reduced by 2 5 mg/week to a maintenance dose of 10 mg/day Azathioprine was given in maximum tolerable doses of 0–3 mg/kg/day dependent on leucocyte count

Additional parameters

All the treated patients were followed at regular examinations both during treatment and in the subsequent control period to death or Dec 31 1974 In conjunction with each treatment as well as two and four weeks after completion the following variables were measured leucocyte count leucocyte differential count (granulocytes eosinophil cells lymphocytes and monocytes) erythrocyte count reticulocyte count and thrombocyte count. Before treatment after 25 000 rad after 50 000 rad and two weeks and four weeks after the completion of ECIB the following parameters were also measured haptoglobin erythrocyte osmotic resistance immunoglobulins IgG IgA IgM IgD and IgE complements C 3 and C 4 and the plasma proteins albumin α 1 α 2 β- and γ-globulin In the subsequent observation period lymphocyte counts were made regularly at increasing intervals

In the middle of the investigation period the same variables (except erythrocyte reticulocyte and thrombocyte counts and osmotic resistance) were determined for comparative purposes in conjunction with hemodialysis in ten *control patients Determinations were made at the same intervals and over a period (55 6±5 8 days) corresponding* to that of +ECIB series These patients were selected as the only non transplanted control patients at the time Immunoglobulins complements and plasma proteins were redetermined in the control patients after a further two to three months so that the reproducibility of serial measurements of these variables could be evaluated

In an evaluation of the influence of a single treatment on the parameters investigated leucocytes lymphocytes immunoglobulins and complements were determined be*fore and after 1.5 3 4 5 and 6 hours of simultaneous* hemodialysis and ECIB in five cases

IgG IgA IgM and IgD as well as C 3 and C 4 were determined by rocket immunoelectrophoresis according to Laurell IgE was determined by radioimmunoassay and plasma proteins by paper electrophoresis All samples at the start of hemodialytic and ECIB treatment were taken before the initial heparinization

Leucocyte counts were made on a Coulter counter and all differential counts were performed by the same technician throughout the investigation period In a control experiment in which nine consecutive blood samples were drawn from the same patient and of which eight were prepared for leucocyte counts and differential counts while the ninth was used to prepare a leucocyte count and 2×8 smears for differential counts on two different days the coefficient of variation calculated for leucocyte counts was 3 7% and for lymphocyte counts 9 7% and 8 5% (intraspecimen and interspecimen respectively)

The collected data were processed in an IBM 370 computer (Fortran programme) and graphs of the variables for each patient drawn using an automatic plotter with the radiation dose in rad as abscissae For WBC and RBC additional curves were drawn with the number of irradiated blood volumes as abscissae For long term observation of lymphocyte counts after the completion of treatment further curves were drawn with time in days as abscissae Altogether 1 008 graphs were obtained for closer evaluation

Erythrocyte survival time

A radio-chromium method (^{51}Cr) was used as described by the International Committee for Standardization in Hematology (14)

Measurements were made in conjunction with ECIB treatment of eight patients before during and after the period of treatment

Table V *Survival times for treated and control patients and grafts in relation to start of observation period renal allotransplantation graftectomy death or Dec 31 1974 (mean ±1 S D and range)*

	+ECIB	0-ECIB	P^*
From allocation in +/0-ECIB groups to death or Dec 31 1974	446±345 (2–1 226) n=55	680±373 (5–1 276) n=46	<0 05
From allocation in +/0-ECIB groups to RAT	221±218 (1–903) n=25	280±244 (45–1 156) n=28	<0 01[b]
From RAT to start of post RAT ECIB	6±3 (2–14) n=20	–	–
From RAT to first rejection episode	93±121 (4–350) n=13	58±120 (2–519) n=18	0 01< p<0 02
From RAT to graft ectomy (only graft ectomized pats)	70±99 (6–244) n=5	113±215 (7–777) n=12	n s
From RAT to death or Dec 31 1974 (only RAT pats)	345±294 (7–994) n=25	517±329 (43–1 201) n=28	<0 01

* Mann Whitney probability test n s =not significant
[b] Clinical relevance=prolongation by two months

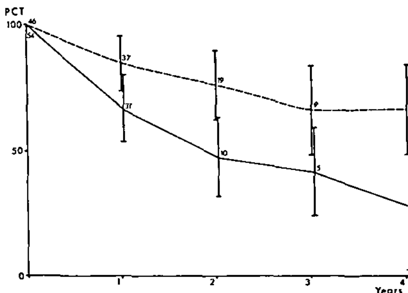


Fig 2 Decrement curve for survival in treated (—) and control group (- - -) from random allocation to death or Dec 31 1974 Figures on the curves give the number of patients in each period and the vertical bars indicate 1 S D The curves are calculated from the dates of inclusion and exclusion from the material *A χ^2 test for comparison be*tween the two curves shows that they are significantly different

RESULTS

During the period of the investigation 1971–74 (3 5 y) 101 patients were included in the analysis 55 in *the treated group and 46 in the control group* Their sex and age distribution and primary kidney disease are detailed in Table II There are no significant differences between the two groups

Sequential analysis

Of the 55 +ECIB patients and the 46 0-ECIB patients only 17 and 22 respectively were included in the analysis The reasons for exclusion of 38 and 24 patients *respectively from this part of the in*vestigation are described in Table I There was a preponderance of deaths in the +ECIB group ($p=0\ 06$) and similarly a larger number of exclusions from this group ($p=0\ 04$) Data concerning the ECIB treatment given are shown in Table VI

There were thus 17 pairs in the period of observation but 12 of them were tied pairs (in seven pairs both patients rejected the graft and in five pairs neither patient) so that only five preferences were entered in the diagram (Fig 1) Thus no conclusion was reached in the sequential analysis Whether the treatment has an effect or not cannot be decided but it seems reasonable to conclude that there certainly was no dramatic effect The sequential analysis was stopped before the result line intersected the limits of the diagram because the experience gained in the other parts of the investigation indicated that ECIB had a harmful effect

ECIB and RAT (additional results)

The following results refer to data shown in Tables III–V and decrement curves for survival presented in Figs 2–4 They are based on all 101 patients

Patient survival from allocation to the two groups to Dec 31 1974 or death was significantly reduced in the +ECIB group (Table V $p<0\ 05$ Fig 2 $\chi^2=3\ 6–8\ 4$) and there were more deaths in the +ECIB than in the 0-ECIB group (Table III $p=0\ 01$)

The time from allocation to groups until RAT was shorter for the +ECIB than for the 0-ECIB group (Table V $p<0\ 01$) *but this is of little clinical rele*vance being on an average only two months There were fewer transplanted patients in the +ECIB than in the 0-ECIB group (Table IV $p=0\ 05$) which is probably related to the larger number of deaths in the former group

There were no differences in the degree of matching used for transplantation in the two groups (Table IV)

The following results concern the transplanted patients in the two groups

There was no significant difference in the number of rejections before day 60 after RAT (Table III $p=0\ 17$) in accordance with the result of sequential analysis The time from RAT to first rejection episode was prolonged in the +ECIB group (Table V $p<0\ 02$) by an average of 35 days which does have some clinical relevance because the post operative period is critical in other ways However

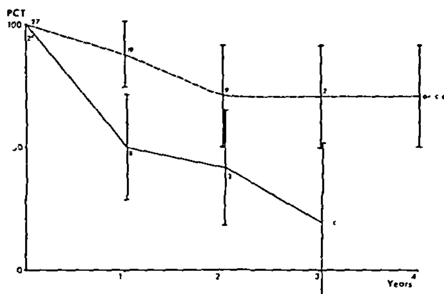


Fig 3 Decrement curves showing survival from RAT to death or Dec 31 1974 calculated from the dates for inclusion and exclusion from the material The figures on the curves give the numbers of patients in each period and the vertical bars give 1 S D A χ^2-test of comparison of the two curves shows that they are significantly different

there was no difference in the total number of rejections in the two groups (Table III $p=0\ 15$) and there was an increased number of cases with ≥2 rejections (Table III $p=0\ 05$) in the +ECIB group The time from RAT to graftectomy was the same in the two groups (Table V n s) even though there were fewer graftectomies in the +ECIB than the 0-ECIB group (Table III $p=0\ 05$) This relationship is probably due to the fact that more deaths occurred after RAT in the +ECIB group than in the 0-ECIB group (Table III $p=0\ 03$) while survival from RAT to graftectomy or death was the same in the two groups (Fig 5 $\chi^2=0\ 9$–$1\ 3$) Survival time from RAT to death was on the other hand significantly shorter in the treated group as shown in Fig 3 ($\chi^2=7\ 1$–$10\ 4$) and Table V ($p<0\ 01$)

Additional parameters

The graphs showed large individual variations as a result of the patients different immune status at the start of treatment and it was therefore considered impossible to operate with average curves for the various parameters Instead a non parametric evaluation of the results was chosen the curves being classified according to an increasing decreasing or unchanged tendency The results obtained in this way are shown in Table VI

The most important results seem to be unaltered leucocyte granulocyte eosinophil and monocyte counts in the two groups ($p=0\ 09$) and a reduced lymphocyte count in the treated group in contrast to the control group ($p=0\ 003$)

In comparisons between counts at the beginning and at the end of ECIB treatment (both in relation to radiation dose and to irradiated blood volumes) lymphocyte counts decreased in all patients except one However the course of this change between the two values varied greatly as shown in Fig 5 This is also an example of the impossibility of calculating average curves which have any basis in reality

There were no characteristic relationships for immunoglobulins complements or plasma proteins in the +ECIB group and no differences between the two groups

Additional serial measurements of these parameters in control patients were made 2–3 months after the first so that the validity of such measurements made in the course of treatment could be evaluated Sixty five double series of measurements were made and of these only 28 had a similar course Of the 35 immunoglobulin and complement series only 8 had a similar course

In measurements performed during a single combined hemodialysis and ECIB treatment for 0–6 hours there were no significant changes for leucocytes lymphocytes immunoglobulins or complements Erythrocyte counts decreased in 25 of 35 patients (25/35) (usually after 20 000–25 000 rad) whereas there were no changes in reticulocyte count (29/35) osmotic resistance (15/19) haptoglo-

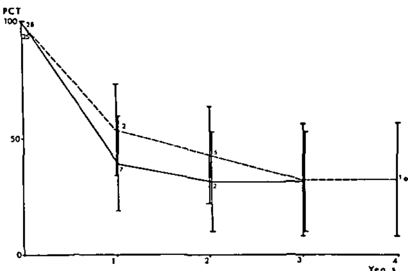


Fig 4 Decrement curves of graft survival from RAT to graftectomy death or Dec 31 1974 calculated from dates for inclusion and exclusion from the material The figures on the curves give the numbers of patients in each period and the vertical bars 1 S D A χ^2 test of comparison of the curves shows that there is no significant difference between them

bin (14/19) erythrocyte survival time (7/8) and thrombocyte count (17/21) Erythrocyte counts showed a similar decrease in relation to numbers of irradiated blood volumes (21/34)

Long term results

During the first months after conclusion of treatments lymphocyte counts were found to increase in 9/31 decrease in 6/31 and remain unaltered in 16/31 For IgG IgA and IgM there was a return to initial values in those cases which had shown a decrease This tendency was less pronounced for IgD IgE C 3 C 4 and γ globulin In long term observations (up to 1 276 days Table V) unaltered low values were seen in 26/38 and increasing values in 12/38

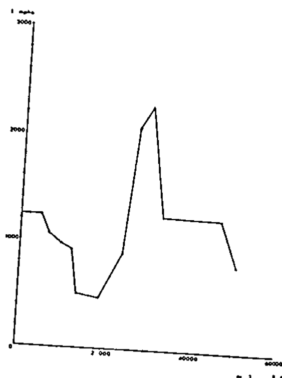
DISCUSSION

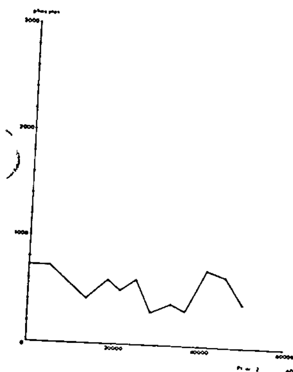
The effect of ECIB on the peripheral blood and thus its possible immunosuppressive effect has been the subject of intensive study A series of animal experiments (calves goats) mainly by Cronkite et al (7–11) showed a selective long term lymphocytopenia of the peripheral blood with some effect on erythrocytes by CD over about 30 000 rad but without effect on thrombocytes (13) A number of studies showed T cell depletion of lymph nodes (7 11) and a longer graft survival for skin and kidney grafts

This controlled investigation using non parametric statistical methods in the comparisons shows that ECIB using the TD and CD described gives a long term selective lymphocytopenia with a small and non limiting hemolysis after 25 000–50 000 rad The treatments did not seem to affect either thrombocyte counts or immunoglobulins complements and other plasma proteins but the individual variations of the latter are so large that they cannot be used to evaluate the effect of treatment A single ECIB treatment did not give demonstrable lymphocytopenia but the simultaneous heparinization and consequent mobilization of lymphocytes from reserves in the central lymphoid tissue must also be taken into account

The degree of lymphocytopenia in individual patients varied greatly so that lymphocyte counts after the treatment series ranged from 6 to 75% of initial values This is a very large variation and because it is normally distributed (non significant deviation from normal distribution curve χ^2 test $0\ 50>p>0\ 40$) it is to be expected that all degrees of lymphocytopenia from 0–100% of initial values can be obtained Thus this study cannot provide support for the existence of some special lymphocyte population with a specially fast turnover which keeps pace with the lymphocytopenia induced by irradiation or of a population of special lymphocytes resistant to irradiation—in contrast to the results of Weeke (20–23) and Weeke and Hess Thaysen (24) In previous large investigations by Persson et al (15 16) and Weeke (20–23) a positive effect of ECIB was seen in the form of fewer rejections and increased graft survival In an expanded







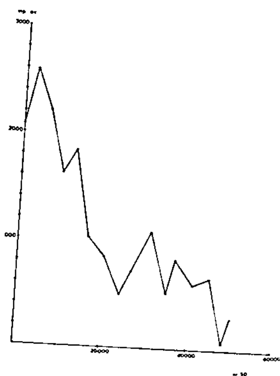


Fig 5 Four different types of lymphocyte depletion curves during ECIB

Table VI *Non parametric judgement of the course of leucocytes lymphocytes immunoglobulins complement components and some plasma proteins in treated and control patients*

The course of the curves is judged as increase (↑) decrease (↓) or unchanged (=) in the fractions the numerator gives number of observed courses (↑ ↓ or=) and the denominator the number of observed patients

	+ECIB			0-ECIB		
	↑	↓	=	↑	↓	=
Leucocytes	2/41	2/41	37/41*	2/9	1/9	6/9*
Lymphocytes	0/41	32/41**	9/41	4/9	1/9 *	4/9
IgG	10/41	11/32	12/32	4/8	0/8	4/8
IgA	5/26	11/26	10/26	1/8	2/8	5/8
IgM	9/32	13/32	10/32	2/8	1/8	5/8
IgD	5/15	4/15	6/15	–	–	–
IgE	1/16	7/16	8/16	–	–	–
C 3	14/34***	9/34	11/34	0***	4/8	4/8
C 4	12/34	10/34	12/34	1/8	5/8	2/8
Albumin	0/35	0/35	35/35	2/8	2/8	4/8
α_1 globulin	4/32	5/32	23/32	0/8	1/8	7/8
α_2 globulin	4/31	9/31	18/31	0/8	1/8	7/8
β globulin	15/29	2/29	12/29	0/8	0/8	8/8
γ globulin	12/23	1/23	10/23	4/8	2/8	2/8

*p=0 09 **p=0 003 ***=0 03 all other comparisons= n s (Statistical evaluation by Fisher's exact test)

material (21) however no increased graft survival was found

In this study which differs from previous studies in being a controlled investigation in the form of a fixed dose trial these advantages of ECIB could not be demonstrated Apart from a delay in the timing of the first rejection in the treated group only a series of negative properties of ECIB in the treatment of kidney transplantation could be demonstrated and they will not be repeated here

As the doses chosen for both TD and CD are those normally accepted (and cannot be increased because of the risk of hemolysis) the conclusion must be that ECIB cannot be recommended as an immunosuppressive treatment of uremic patients in conjunction with RAT

The question is thus why the effect of ECIB is missing and what effect if any ECIB has as an immunosuppressive agent

These questions can be elucidated by 1) lymphocytokinetic investigations 2) lymphocyte transformation tests and 3) an investigation of the central lymphoid tissue in conjunction with ECIB

Lymphocytokinetic investigations using chromosome studies and labelled lymphocytes (12 19) have shown that the exchangeable lymphocyte pool in the organism is about 30 times the number of lymphocytes in the peripheral blood It is this quantity of lymphocytes which is affected by ECIB The remaining quantity of lymphocytes in the blood even after large CD does not according to Fields et al (12) consist of special radiation resistant cells and contains both T and B lymphocytes (3 20) These residual cells respond in lymphocyte transformation tests after stimulation with mitogens antigens and allogenic cells Somewhat divergent results exist concerning the effect of ECIB on cellular immune response measured using these tests Rosengren et al (17) demonstrated an effect on PHA response while Weeke (20) found an unaltered PHA response but a reduced PPD and MLC response during ECIB with a return to normal after the treatment is stopped Birkeland et al (4) found that these immune responses during ECIB were very individual and the nature of changes in relation to ECIB was uncharacteristic

While lymphokinetic investigations provide information about the exchangeable *quantity* of lymphocytes they say nothing about whether there is a varying degree of exchangeability in the various lymphocyte compartments and whether these compartments are possibly of different immunological importance While animal experiments (7 9) have shown an often fundamental depletion of lymph nodes especially T lymphocytes the only available (and controlled) human investigation (3) did not show any depletory effect but rather a tendency to increased immunocapacity after ECIB Lymphocyte transformation tests using lymphocytes from lymph nodes excised before and after ECIB have in no way given an unequivocal indication of immunosuppression of the central lymphoid tissue and lymphocytes taken simultaneously from lymph nodes and peripheral blood gave widely divergent results in these tests (3)

Thus even though there does not appear to be a regulating feed back mechanism affecting the *quantity* of lymphocytes this could be the case for the *immunocapacity* of lymphocytes

ACKNOWLEDGEMENTS

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Survival after Portacaval Shunt Who and how?

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ABSTRACT In a series of 74 portacaval shunted patients no statistically significant differences in long term survival or in incidence of postoperative encephalopathy have been observed between electively and emergency operated patients, between patients with slight and moderate impairment of liver function (groups A and B according to Child) or between patients with alcoholic and non alcoholic cirrhosis Patients older than 60 years had a higher risk of postoperative encephalopathy and a border line significantly lower survival rate six months after the operation Among the patients with more than six months' survival, about 50% returned to work

The value of portacaval (PC) shunt has often been questioned even though there is no doubt that it is effective in preventing bleeding from oesophageal varices Its clinical value was questioned when it was shown that prophylactic PC shunt decreases rather than increases the survival rate (4 5 12 19) The explanation of this disappointing finding was that the shunted patients showed an increased rate of hepatocellular failure Since prophylactic shunting means operating on a large number of patients who would never have bled from their varices if left unoperated (16) there still remained the possibility of a beneficial effect of therapeutic shunt Two controlled clinical trials have been reported in recent years both showed a trend towards enhanced survival of the operated patients (13 20) Conn (3) combined the data from these studies and found that the difference came within a hairsbreadth of achieving statistical significance at the 5% level

However many questions still remain unanswered The two studies above were almost completely restricted to patients with alcoholic cirrhosis and thus the value of PC shunt in other forms of cirrhosis is still not clear One may also ask to what extent the American experiences can be applied to a Scandinavian population No controlled Scandinavian study is available and will probably not be performed due to the great difficulties involved Uncontrolled published experiences from Scandinavia are also rare As far as we know none has appeared since 1957 when Ekman published his results in 29 PC shunted cirrhotic patients (7)

Possible advances in the postoperative management of the patient in recent years which may have changed the results of PC shunt was a further reason for the present investigation Other purposes were to study whether there are differences in outcome that can be related to the preoperative degree of liver insufficiency and whether the postoperative long term survival in alcoholic cirrhosis differs from that in non alcoholic cirrhosis Finally we wanted to know the quality of life of the operated patients since conservative treatment is often advocated after variceal bleeding because of fear of encephalopathy or expectance of postoperatively continued alcohol abuse

MATERIAL

The material comprised 74 patients (65 males) who were operated on with PC shunt during 1961–74 in the Sahlgren s Hospital Thirty two shunts were performed as emergency operations (i e the bleeding was not controlled by conservative measures such as vasopressin or the Sengstaken tube) and 42 as elective operations The distribution of emergency and elective operations among the patients classified according to Child (2) and clinical and laboratory data are given in Table I

The etiology of the cirrhosis was considered to be alcoholic abuse in 48 patients Three patients had known chronic active hepatitis and two a history of acute hepatitis Two patients had hemochromatosis one had porphyria cutanea tarda and one probably had a sec

Table I *Clinical and laboratory classification of emergency or electively operated patients with cirrhosis in terms of hepatic functional reserve*

	Liver function groups		
	A	B	C
Emergency operations (*n*)	22	18	2
Elective operations (*n*)	16	13	3
Serum bilirubin (mg/100 ml)	<2 0	2 0-3 0	>3 0
Serum albumin (g/100 ml)	>3 5	3 0-3 5	<3 0
Ascites	None	Easily controlled	Poorly controlled
Neurological disorder	None	Minimal	Advanced coma

ondary biliary cirrhosis In 17 patients the etiology was unknown

In 11 of the 32 emergency operations the PC shunt was performed at the first bleeding episode Nine of the 42 elective operations were performed after the first bleeding

RESULTS

The *postoperative mortality* during 30 days after the PC shunt was 19% in the elective group and 27% in the emergency group In group A the mortality was 16% in group B 23% and in group C 75% (3/4 patients) The causes of the postoperative deaths in the group A patients were circulatory insufficiency shunt with rebleeding anemic liver in ion ileus and in two patients peritonitis

When calculating the *long term survival* the only surviving group C patient who died 10 months after the operation was omitted As shown in Fig 1 the difference in survival between electively and emergency operated patients was small and not statistically significant

Similarly when comparing patients in groups A and B (combined elective and emergency operations) no statistically significant differences between the groups were detected (Fig 2) The survival was almost identical in patients with alcoholic and non alcoholic cirrhosis (Fig 3) No statistically significant differences in survival were detected between patients older than 60 years (mean age 64 7 and 65 5 years for the elective and emergency groups) and patients younger than 60 years (mean age 49 0 and 49 2 years respectively) at the time of the operation neither when considering elective and emergency operations separately nor when the two materials were considered together (Fig 4) However at six months the difference in survival rate was of borderline significance

In the two controlled therapeutic PC shunt studies cited above there was a trend favoring operation in the patients with a single variceal bleeding However in our material the patients with only one major episode of ruptured varices before operation did not survive longer than those with more than one bleeding (Fig 5)

The *causes of death* are given in Table II Twenty three per cent of the deaths were not related to the liver Almost 10% of the operated patients died of renewed variceal bleeding

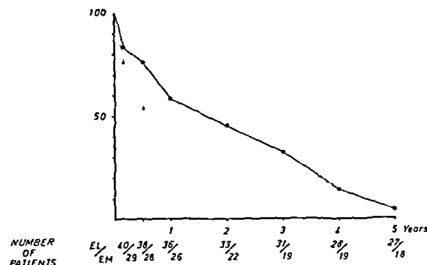


Fig 1 Survival in group A and B patients electively (*EL* —) or emergency (*EM*) operated The figures at the bottom of the diagram indicate number of patients at risk

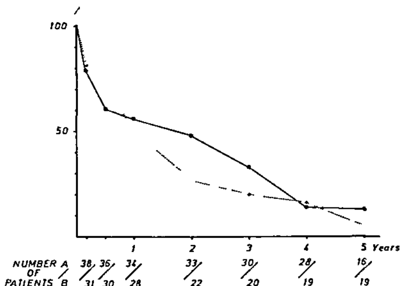


Fig 2 Survival in electively and emergency operated patients in liver function groups A (—) or B ( ) at operation

Portasystemic encephalopathy (PSE) appeared postoperatively in 19 of the 60 patients (30%) who had no PSE prior to the operation and in 11 of the 14 (80%) who had PSE preoperatively (Table III) a difference which is statistically highly significant

In 9 of the patients the PSE was a terminal event of short duration (Fig 6) in 2 patients it was restricted to a short period postoperatively and in 2 patients a single short period of PSE occurred during a 4½ year survival Thus several or prolonged episodes of PSE occurred in 17 patients (23%) 13 of whom had had no PSE before the operation Seven of these 13 patients (54%) were classified as belonging to group A preoperatively There was no difference in the overall incidence of postoperative PSE between patients in group A (29%) and group B (30%) who had no PSE preoperatively The total incidence of postoperative PSE was significantly higher in patients above 60 years of age (63%) at the operation than in younger patients (27%) In those patients who had no PSE preoperatively the age related difference (48 vs 23%) was close to statistical significance

No significant difference in incidence of postoperative PSE was detected between patients with alcoholic and non alcoholic cirrhosis Thirteen of

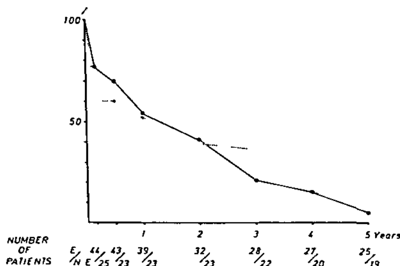


Fig 3 Survival in patients with cirrhosis probably caused by ethanol (*E* —) compared to cirrhosis probably not caused by ethanol (*N E*)

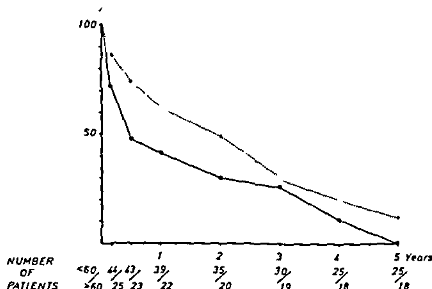


Fig 4 Survival in patients aged >60 (—) at the operation compared to patients aged <60 ( ) at the operation

the alcoholic and six of the non alcoholic patients who survived more than 6 months after the operation had had an occupation before the operation Seven of the alcoholic and three of the non alcoholic patients were able to *return to work* post operatively

An attempt was made to evaluate the effect of *abstinence from alcohol* on survival in those patients with alcoholic cirrhosis who survived the first postoperative month Presumably reliable information was obtained in 29 patients Thirteen of these were probably abstinent postoperatively No differ ... at all existed in survival during the first 2 ... thereafter the groups were too small to permit comparisons In this small material no differences were detected in the incidence of abstinence between group A and group B patients

DISCUSSION

Many difficulties arise in the handling of a patient with bleeding oesophageal varices The greatest is probably the decision to recommend surgery or not Acute surgical intervention with an emergency PC shunt has generally been reported to have a much higher per and postoperative mortality (about 50%) than an elective operation (6 8 17 22) The

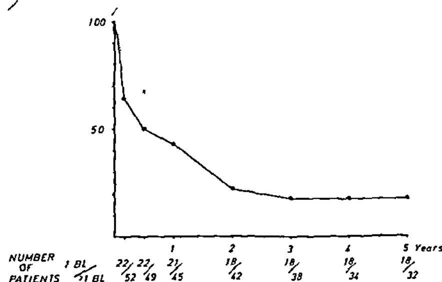


Fig 5 Survival in patients with only one major bleeding episode (*I BL* —) before the PC shunt compared to patients with more than one bleeding (>*I BL*)

results presented in this study differ from those in the literature since the mortality during the first 30 postoperative days was only slightly higher (27 vs 19%) in the emergency group than in the electively operated patients Furthermore the long term survival did not differ between the groups (Fig 1) The reason for this similarity may be manifold an active policy with early operation in those patients who do not respond to conservative measures is probably important for decreasing the emergency mortality Our restrictive attitude to operation in group C patients who are the most likely failures on conservative treatment is probably another important explanation of our comparatively low mortality figures after emergency operations It is therefore our opinion that bleeding group A and B patients who do not respond to conservative treatment should be operated on with minimal delay Optimism with the hope of spontaneous hemostasis is usually deleterious

The decision to recommend surgery or not may be even more difficult in the patient who has just stopped bleeding from esophageal varices It is true that there are studies on large materials indicating a benefit from elective PC shunt However there may be special conditions for the patient in question which can make the doctor hesitate to decide on an operation We shall discuss some of these factors in the light of our present findings

High *age* should reasonably be connected with a higher risk Our survival figures (Fig 4) certainly seem to be more favorable for the younger patients but the difference does not seem deterrently great and in fact did not achieve statistical significance Our impression of a rather small difference between patients below and above 60 years at the operation are in accordance with earlier experiences when comparing patients below and above 40 years (11 13) and below and above 50 years (9)

Another factor which theoretically could be of

Table II *Causes of death*

Mortalities within the first postoperative month given within parentheses

Varceal bleeding	7	(4)
Other GI bleeding	5	(3)
Hepatoma	4	
Hepatic coma	18	(5)
Other causes	10	(5)

Table III *Incidence of postoperative PSE in relation to preoperative occurrence of PSE preoperative liver function age at operation and etiology of cirrhosis*

	Preoperative PSE		No preoperative PSE		Total	
	n	%	*n*	%	*n*	%
Liver function group						
A	0/0	–	11/38	29	11/38	29
B	9/11	82	6/20	30	15/31	48
C	2/3	–	2/2	–	4/5	–
Age at operation (y)						
>60	9/9	100	10/21	48	19/30	63
<60	3/5	60	9/39	23	12/44	27
Etiology of cirrhosis						
Ethanol	9/12	75	9/36	25	18/48	38
No ethanol	2/12	–	10/24	42	12/26	46

importance for survival after operation is *the etiology of the cirrhosis* However our comparison of alcoholics and presumed non alcoholics (Fig 3) did not show any difference in this respect These findings are in accordance with results of comparisons of 3 year survival performed by Foster et al (8) and by Hourigan et al (11) The latter authors however found a lower postoperative 3 year survival rate for chronic active hepatitis than for alcoholic and cryptogenic cirrhosis The number of patients with chronic active hepatitis in the present study was too small to permit special consideration

A moderate preoperative impairment of the *liver function* consistent with a group B classification did not seem to involve a lower survival rate in comparison with group A patients Similar experiences have been reported by Edmondson et al (6) Foster et al (8) and Wantz and Payne (23) On the other hand other investigators have registered greater differences in survival rate between A and B group patients (1 10 14 20 21) This discrepancy in results may at least to some extent be explained by difficulties inherent in the classification system We have repeatedly observed transient derangement of the liver function in connection with bleeding episodes Therefore if results from liver tests were available from the 2 month period preceding the bleeding these values rather than the latest ones have been considered in the classification of the patient If however no earlier test results were available we have had to classify according to the only available data which may have meant that

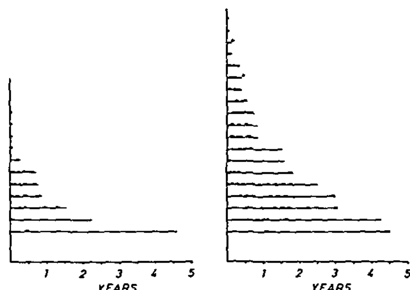


Fig 6 Occurrence of PSE post operatively (■) in patients with (left) and without (right) PSE before the operation + = death

some patients who in a non bleeding state belonged to group A have in fact been classified as belonging to group B On the whole the Child classification system is not ideal but as pointed out by i a Campbell et al (1) no better system is available

The only risk factors for the development of *postoperative PSE* found in the present study were preoperative PSE and high age Our findings in this respect are in accordance with previous reports (11 15) On the other hand the preoperative liver function assessed by the Child classification system did not seem to influence the rate of postoperative which has also been noted by Wantz and ne (23)

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A Comparative Study of the Effects of Cholestyramine and Neomycin in the Treatment of Type II Hyperlipoproteinaemia

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ABSTRACT A comparative study of the effects of cholestyramine and neomycin has been carried out in 35 patients with severe type II hyperlipoproteinaemia Both agents were administered during a period of 18 weeks, the daily dosages being 12, 16 or 20 g cholestyramine and 1, 1 5 or 2 g neomycin The mean decrease in cholesterol concentration was 22% with cholestyramine and 23% with neomycin There was no difference in effect between the two agents and between the doses used No significant influence on triglyceride concentration and on body weight was observed No signs of deficiencies in fat soluble vitamins were found Anticoagulant requirements increased during cholestyramine medication No signs of hyperchloraemic acidosis were observed during treatment with cholestyramine Cholestyramine was tolerated less well than neomycin it had to be discontinued in 8 cases Neomycin was not tolerated by 3 patients The majority of the patients preferred neomycin

Type II hyperlipoproteinaemia is associated with a markedly increased risk of atherosclerosis (30) Since lowering of the plasma lipids can reduce the morbidity and mortality of cardiovascular diseases (22) treatment of type II hyperlipoproteinaemia seems indicated In severe cases in which dietary measures alone produce no adequate effect drug treatment should be instituted

The most marked effect seems to be obtained with agents which interrupt the enterohepatic circulation of bile acids (10) such as the synthetic resins cholestyramine colestipol or DEAE sephadex The faecal loss of bile acids is compensated by conversion of cholesterol to bile acids causing the plasma cholesterol level to decrease in spite of a possibly increased cholesterol production (20) A disadvantage of these agents is that very large doses are required Neomycin is a possible alternative (6 28) Its mechanism of action is probably based on its pronounced basic character which enables it to antagonize micelle formation in the intestinal lumen (31) Possibly the reabsorption of bile salts and cholesterol is diminished as a result (21)

The purpose of this study was to compare the therapeutic and side effects of cholestyramine and neomycin in the same group of patients with severe type II hyperlipoproteinaemia A preliminary study solely about the effect of cholestyramine in a smaller group of patients has been published earlier (29)

PATIENTS AND METHODS

The study was carried out in 35 out patients 14 men and 21 women with ages ranging from 18 to 64 years (mean ±S D 45±14) All had primary type II hyperlipoproteinaemia with plasma cholesterol levels of at least 10 mmol/l with normal or only slightly elevated triglyceride levels and with type II patterns on cellulose acetate electrophoresis of plasma lipoproteins

A control period of at least 9 weeks was followed by an 18 week period of treatment with either cholestyramine or neomycin A 6-week period without medication followed whereupon the other agent was administered during 18 weeks The two drugs were alternately and therefore equally often prescribed as first agent One patient first given neomycin subsequently did not receive cholestyramine because of an intercurrent disease This means that 34 patients received cholestyramine in daily doses of 12 16 or 20 g Four patients disappeared from the follow up after the cholestyramine period which means that 31 patients received neomycin in daily doses of 1 1 5 or 2 g

Table I *Effect of cholestyramine and neomycin during 18 weeks in patients with type II hyperlipoproteinaemia*

Dose (g/d)	No of pats	Plasma cholesterol (mmol/l) Control[a]	Therapy[b]	Mean decrease (%)	Plasma triglycerides (mmol/l) Control[a]	Therapy[b]	Mean decrease (%)
Cholestyramine							
12	8	11 0±0 7	8 7±0 5	21***	2 53±1 17	2 41±0 93	5 N S
16	6	11 6±2 4	8 7±1 3	25*	2 20±0 48	2 00±0 32	9 N S
20	12	12 1±2 3	9 4±2 4	22*	2 07±0 69	2 10±1 20	0 N S
Neomycin							
1	8	11 8±1 7	9 0±1 8	24**	2 39±0 76	2 34±1 00	2 N S
1½	10	11 5±1 8	9 0±1 9	22	2 03±0 89	1 82±0 88	11 N S
2	10	11 7±2 3	9 0±1 8	23**	2 42±0 99	2 02±0 83	16 N S

[a] Mean±S D of 3 observations [b] Mean±S D of the last 4 observations during treatment
* $p<0.05$ ** $p<0.01$ *** $p<0.001$ N S =not significant

Both agents were taken during meals All patients were on a diet rich in unsaturated fatty acids throughout the control periods and the periods of medication No attempt was made to calculate the dietary intake of polyunsaturated fatty acids and total fat

At 3 week intervals venous blood samples were drawn without stasis after an overnight fast for determination of cholesterol and triglyceride Body weights were checked and patients were asked about drug adherence and side effects Cholesterol was estimated by a modification of the method of Huang et al (15) not proceeded by lipid extraction The triglyceride concentration was determined enzymatically according to Eggstein and Kreutz (4)

In view of possible interference with the absorption of fat soluble vitamins the following investigations were made During medication the normotest according to Owren was determined at least 4 times in all patients using no anticoagulants The patients on anticoagulants were evaluated to establish whether changes in dosage were necessary Serum vitamin A vitamin E alkaline phosphatase calcium and inorganic phosphate concentrations were determined at the start and end of each period of medication while tubular reabsorption of phosphate and the 24 hour urinary excretion of calcium hydroxyproline and indican were determined only at the end of each period Vitamin A was estimated by a modification of Paterson s method (24) A modification of the method of Emmene and Engel (5) was used for vitamin E Urinary hydroxyproline was determined by a modification of the method of Prockop and Udenfriend (25) Urinary indican excretion was measured to establish whether neomycin might disturb the intestinal flora so significantly as to give rise to bacterial overgrowth of the small intestine (prompting a changed bile salt metabolism) The method of Müting and Burgard (23) was used to ascertain urinary indican excretion The faecal fat concentration was determined by a modification of the method of Van de Kamer et al (17) The pH of blood was estimated in a number of patients because the occurrence of hyperchloraemic acidosis resulting from exchange of chloride ions against bile salts during cholestyramine medication has been reported (27) Renal and hepatic function and blood counts were regularly checked

RESULTS

Acceptability of the drugs

Of the 34 patients who received cholestyramine 26 completed the 18 week period of medication In 5 patients the drug was discontinued because of nausea and abdominal cramps 2 patients regarded regular ingestion and check ups as too inconvenient and 1 patient reported bleeding from preexistent haemorrhoids due to persistent constipation Four patients complained of moderate constipation during treatment with this drug

Neomycin was used throughout the 18 week period by 28 patients Three patients did not tolerate this drug (abdominal cramps and diarrhoea) A few patients reported frequent bowel movements during the first few days on neomycin administration but this complaint ceased spontaneously within a week Four patients occasionally experienced heartburn during neomycin

On inquiry only 8 patients expressed a preference for cholestyramin while 20 preferred neomycin

Lipid lowering activity

For calculation of the fall in cholesterol the last four observations in each period of medication were used In all patients using cholestyramine a decrease in plasma cholesterol was found which

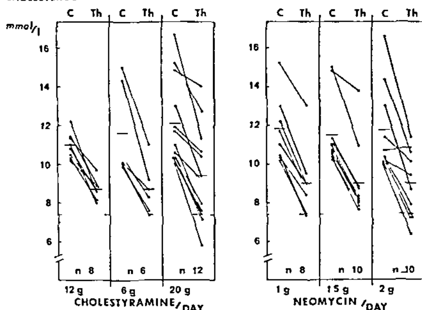


Fig 1 Mean plasma cholesterol levels during control (*C*) and therapy (*Th*) periods A horizontal dash ind cates the mean value for each group of patients the upper l mit of the normal range (7 3 mmol/l)

ranged from 5 to 42% (mean 22%) In 4 patients who ingested 20 g/day the fall (5 11 11 and 13% respect vely) was not s gnif cant (Student s *t* test) With neomycin the decrease in cholesterol ranged from 0 to 37% (mean 23%) In ? pat ents who ingested 2 g da ly there was no s gnif cant fall (0% and 7% respect vely) The effects on the plasma cholesterol level of cholestyram ne and neomyc n in the various doses in all pat ents during 18 weeks of treatment are shown in Table I and F g 1

The fall of plasma cholesterol could not be ascribed to weight reduction In only 10 of 54 periods of drug treatment was there a reduct on of body weight of more than 1 9 kg (mean ? 8) Th s was observed in 7 patients during treatment w th neomycin and in 3 while on cholestyramine The mean reduct on of cholesterol n these 11 periods (?3%) d d not d ffer from the mean reduct on in all pat ents

Cholestyram ne and neomyc n exerted no s gn f cant influence on the triglyceride concentra t on (Table I)

Influence on the absorpt on of fat and fat sol ble an ns

During a period of cl n cal observation after 18 weeks of drug treatment fat absorpt on as stud ed n 4 pat ents The faecal fat excret on n ? pat ents using 20 g cholestyram ne da ly amounted to 8% and 16% of the d etary fat respectively (normal value<6%) The correspond ng values n 2 patients ingest ng 1 g and 2 g neomycin daily were 3% and 2% respect vely

In the pat ents receiving no ant coagulants the normotest accord ng to Owren rema ned normal during both per ods of med cat on Pat ents on anti coagulants requ red a larger dose to maintain opti mal hypocoagulab l ty (5–11% thrombotest act v

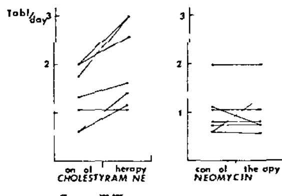


Fig 2 Mean daily number of ant coagulant tablets neces sary to maintain op mal hypocoagulabil ty before and during therapy w th cholestyramine and neomycin

Table II *The absence of hyperchloraemic acidosis and hypercalciuria during treatment with cholestyramine (mean±S D)*

	Control (n=15)	Neomycin (n=12)	Cholestyramine (n=15)
Blood pH	7 35±0 02	7 34±0 04	7 36±0 03
Base excess (mmol/l)	−1 2±1 5	−1 0±1 9	−0 4±2 0
Plasma chloride (mmol/l)	103±2	105±3	105±2
Calciuria (mmol/d)		4 4±1 5	4 9±1 6

ty) during cholestyramine medication During neomycin medication there was no need to change the dose of the anticoagulant (Fig 2) Normal serum vitamin E and vitamin A levels were found in all patients During treatment normal values were found for plasma calcium and inorganic phosphate alkaline phosphatase activity tubular reabsorption of phosphate and urinary excretion of calcium and hydroxyproline

Other side effects

No signs of hyperchloraemic acidosis were observed during cholestyramine medication (Table II) The excretion of indican was during cholestyramine medication 84±26 mg/24 h (mean±S D) during neomycin 85±28 mg/24 h (normal value<100 mg/24 h) Renal function liver function and blood counts remained normal with either agent

DISCUSSION

Our results show that neomycin as well as cholestyramine can lower the plasma cholesterol level in patients with severe type II hyperlipoproteinaemia At the first check up after 3 weeks medication the plasma cholesterol as a rule had already attained the decreased level at which it remained during the entire treatment period No difference in cholesterol lowering effect between cholestyramine and neomycin was found nor was a difference found between the effects of various doses of each drug In a recent review of the literature Grundy (10) found no evidence of a relation between dose and effect of cholestyramine Using neomycin Samuel et al (28) obtained a mean decrease of 22% with doses ranging from 0 5 to 2 0 g daily, Miettinen (21) achieved a reduction of 23% with 1 5 g and Faergeman (6) reported the same mean reduction with 2 g daily In our study we found no difference in effect between daily doses of 1 0 1 5 and 2 0 g It seems to be worthwhile to investigate the effects of even smaller doses of cholestyramine and neomycin

In this study there was no relation between the absolute decrease in cholesterol concentration and the baseline level After discontinuation of the medication the plasma cholesterol concentration as a rule returned to the baseline level after 3–6 weeks In the patients with high plasma cholesterol levels the decrease produced was not sufficient to attain a level generally regarded as normal (Fig 1) Larger doses of cholestyramine however give rise to steatorrhoea (13) and larger doses of neomycin can cause mucosal changes (3)

At the dosages used we have observed no indications of deficiency in fat soluble vitamins Unlike other investigators (14) who reported abnormal prothrombin times we obtained normal normotest values during cholestyramine as well as during neomycin medication In our study the patients on anticoagulants who received neomycin required no change of anticoagulant dosage to maintain optimal hypocoagulability In this respect neomycin differs from cholestyramine which is assumed to have the ability to bind anticoagulants (11) Although neomycin antagonizes micelle formation in the intestine it evidently exerts no discernible influence on the absorption of anticoagulants

The parameters of calcium metabolism we have studied remained normal during cholestyramine as well as during neomycin medication There have been no reports on osteomalacia during cholestyramine and neomycin medication given in order to lower cholesterol levels At a dosage of 32 g cholestyramine Runeberg et al (27) found a slight decrease in the pH of blood and urine along with an increased urinary calcium and chloride excretion We observed neither a significant increase in calcium excretion nor any signs of hyperchloraemic acidosis possibly because we used smaller doses of cholestyramine so that the supply of chloride ions was smaller

When given parenterally neomycin produces marked nephrotoxic and ototoxic effects However since orally given neomycin is hardly absorbed the risk of intoxication is minimal Audiological check ups were performed (by Dr R T R Wentges

and his colleagues at the Department of Otorhino-Laryngology) in 12 of our patients who have been on neomycin more than 1 year The audiograms showed no abnormalities Nevertheless 13 in stances of deafness following oral neomycin medi cation have been reported (1 7 8 9 12 16 18 19 26) In 6 of these cases renal function was di minished (1 9 19 26) and a cumulative effect may have been involved So neomycin should be con sidered contraindicated in cases with diminished re nal function In the other cases dosage and dura tion of medication differed widely In some of these patients extensive inflammation of the intestinal mucosa (7 8 18) may have resulted in increased absorption Recently however Breen et al (2) found no difference in absorption between normal subjects and those with inflammations in the diges tive tract

As stated before neomycin proved to be as effec-tive as cholestyramine and in contradistinction to Faergeman s results (6) caused fewer subjective side effects and was tolerated better Most of our patients preferred neomycin to cholestyramine No signs of malabsorption were found during neomycin medication with a daily dosage of 2 g In view of these findings neomycin would seem to be an ac ceptable alternative to cholestyramine in the treat ment of type II hyperlipoproteinaemia

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Mitotic Activity in Acute Promyelocytic Leukaemia and Leukaemoid Reactions

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ABSTRACT Bone marrow smears from 6 untreated patients with acute promyelocytic leukaemia (APL) and from 6 patients with leukaemoid reactions (LR) have been compared with smears from healthy controls The mitotic indices of the granulopoietic precursor cells were significantly lower in the APL group and significantly higher in the LR group, both compared with the normals Mitotic countings seem to be of diagnostic value for distinguishing APL from conditions simulating this disease

Acute promyelocytic leukaemia (APL) severe infections and acute agranulocytosis in the early recovery phase may sometimes produce clinical and haematological pictures which are difficult to separate All these conditions require early recognition and urgent treatment In 1973 Urasinski (20) found abnormally low mitotic indices in 4 cases of APL and Pisciotta (12) stated that the patients with acute agranulocytosis often have an intense mitotic activity of the bone marrow cells

The aim of the present work was to investigate whether the mitotic activity of the granulopoietic precursor cells viz the myeloblasts the promyelocytes and the myelocytes in the bone marrow of APL patients differed significantly from that of patients of the types mentioned above with conditions simulating this disease with immature myeloid cells in the peripheral blood and a large proportion of promyelocytes in the bone marrow The non leukaemic conditions are referred to here as leukaemoid reactions (LR)

MATERIAL AND METHODS

The investigations described below were performed immediately after the first admission

Patients

APL Six patients 3 women and 3 men aged 21-72 were examined Hb 6 7-12 8 g/100 ml WBC 780-31700 platelets 8000-180000 and ESR 4-145 mm Five of the patients had a marked hypofibrinogenaemia All the patients died within 20 days The autopsies showed haemorrhagic lesions and leukaemic infiltrates in every case

LR Six patients with severe infections 1 woman and 5 men aged 4-91 were examined Hb 10 9-14 5 g/100 ml WBC 600-4000 platelets 10000-170000 and ESR 43-87 mm Four of the patients made a complete recovery with normalization of the bone marrow morphology within one month Two patients died less than 24 hours after admission to the hospital One of them was a 91 year old woman Blood cultures showed growth of E coli Autopsy revealed an ulcerative proctitis but no leukaemic infiltrates The other patient who died was a 72 year-old man with acute cholecystitis and pyelonephritis Blood cultures showed growth of Pseudomonas Autopsy showed no signs of leukaemia

Controls 15 probands 19-82 years old without perceivable haematologic disorders and with clinical diagnoses such as spondylolisthesis cervical disc prolapse adipositas psychiatric disorders and unverified hypogonadism served as controls Hb 12 1-16 6 g/100 ml WBC 2200-8300 and ESR 2-23 mm

Examination of bone marrow smears Bone marrow was obtained by conventional sternal puncture and smears were stained with May-Grunwald-Giemsa A differential count of 1000-2500 nucleated cells was performed and the cells were classified according to Heilmeyer and Begemann (8) and Sjogren (17)

Mitotic indices

APL group 8060-25000 granulopoietic precursors were counted and 20-61 mitoses were found

LR group 6920-9690 precursors were counted and 109-221 mitoses were found

Controls 2480-4960 precursors were counted and ?8-68 mitoses were found

Owing to the very low mitotic activity of the leukaemic cells it was not possible to calculate separate indices for the myeloblasts and the myelocytes and these cells representing the total proliferative compartment were accordingly pooled

Table I *Bone marrow data and mitotic indices from 6 APL and 6 LR patients and from 15 controls*

MB=myeloblasts PMC=promyelocytes MC=myelocytes (expressed as % of all nucleated cells) Mitotic index expressed as % of MB+PMC+MC

Age (y)	Sex	MB	PMC	MC	Auer rods	Mitotic index
APL patients						
21	♀	1 1	86 5	2 7	+	0 19
22	♂	0 4	85 2	1 9	+	0 21
39	♂	2 2	69 1	3 6	+	0 22
46	♂	2 2	80 0	1 5	+	0 31
72	♀	1 5	76 0	3 6	+	0 34
63	♀	2 6	85 8	1 1	+	0 43
LR patients						
72	♂	8 6	55 5	1 6	–	1 25
82	♂	2 9	32 5	17 9	–	1 34
7	♂	2 9	43 1	6 2	–	1 55
4	♂	8 6	21 9	26 9	–	1 58
76	♂	2 1	67 1	5 9	–	1 97
91	♀	3 6	35 1	3 9	–	2 50
Controls						
Range		1 4–3 6	1 2–4 4	7 7–18 0	–	0 93–1 37
Median		2 2	2 8	12 5	–	1 13

RESULTS

The bone marrow data from the patients and controls are presented in Table I

The median mitotic indices for the APL and LR oups and the controls were 0 27%, 1 57% and 13% respectively The difference between the APL and the LR group was significant ($p<0\ 002$ Mann Whitney two-tailed U test) The difference between the APL group and the controls was also significant ($p<0\ 002$) The mitotic indices of the LR patients were significantly higher than those of the controls ($p<0\ 02$)

DISCUSSION

The early diagnosis of APL is sometimes very difficult to make and there are no distinct clinical criteria for a positive diagnosis (6 13) Further more marrow reactions in severe forms of infections and acute agranulocytosis may produce the clinical and haematological picture of a myeloid leukaemia (2 4 8 11, 14) Hypofibrinogenaemia thrombocytopenia and haemorrhagic manifestations are common in APL but may occur in other forms of acute myeloid leukaemia and non haematological disorders (1–7, 9 13, 18) High serum levels of vitamin B_{12} are common—one of our patients with APL had 25 000 ng/l—but this is also the rule in chronic myeloid leukaemia (6 13)

Various morphological abnormalities of the promyelocytes in APL have been described The cells are heavily granulated, with a heterogeneity of the granule population (1, 4, 6 18 19) Rod and splinter forms of the granules are common thus forming faggots of cytoplasmatic inclusions like Auer rods (3, 4 6 7 18 19) These abnormalities seem to be rather specific for the APL The nucleoli in the promyelocytes of the APL patients are sometimes difficult to observe in light microscopy (6) but they are found to be abnormally large in electron microscopy (19) However, large nucleoli are also found in the pleomorph precursors observed in the recovery phase of acute agranulocytosis (8 11 14) thus giving no diagnostic significance

In the present cases of APL the mitotic indices were extremely low The median value was 0 27%, which is similar to the value of 0 28% found by Urasiński (20) These indices are significantly lower than those of the controls and those of normals published by others (10 15 16) On the other hand the LR patients had abnormally high mitotic indices To some extent these raised indices can be explained by larger proportions of immature precursors viz myeloblasts and promyelocytes which are known to have higher mitotic indices than the myelocytes (10 14 15 16)

The present data indicate that mitotic countings may serve as a diagnostic tool in cases of leucopenia with a shift to the left within the granulopoiesis

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Haematologic Adaptation in Patients with Chronic Bronchitis and Pulmonary Insufficiency

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ABSTRACT The relationship between respiratory insufficiency, expressed by gas tensions in blood and bone marrow, and haematologic adaptation has been studied in 82 men with chronic bronchitis and persistent breathlessness for at least one year For the group as a whole and for various subgroups a linear correlation was demonstrated between arterial hypoxia and Hb concentration, haematocrit, blood volume Hb mass and erythrocyte volume, respectively The increase in Hb concentration compensated for the fall in arterial oxygen saturation Only for one subgroup, with a pH difference between arterial and venous blood ≥0 08, was no correlation found between the degree of hypoxia and Hb concentration The haematologic parameters correlated significantly better with arterial oxygen tensions than with oxygen tensions in the bone marrow There was no indication that decreased oxygen supply to the bone marrow led to the increased erythrocyte and Hb production in patients with arterial hypoxia caused by chronic bronchitis

Normal people living at a high altitude develop polycythaemia The individual variation is considerable but generally there is a correlation between the degree of polycythaemia and the reduction in the arterial oxygen saturation so that the arterial oxyhaemoglobin concentration remains close to normal (17 18) In patients with chronic pulmonary disease and hypoxia at sea level the corresponding values for haemoglobin concentration erythrocyte count and haematocrit generally have been found to be lower or normal (1 7 12 14 19 29 33) This could be due to an increase in total red cell volume being masked by an increase in plasma volume (29 33) However the total red cell volume and the haemoglobin mass were often found to be less than expected (12 19 33) a suboptimal haematologic response was shown despite normal erythrocyte life (7 12 29 33) and apparently adequate production of erythropoietin (6 7 23 33) Only in a group of ex miners with chronic bronchitis and/or silicosis did a close correlation between arterial oxygen saturation and the haematologic data point to an adequate polycythaemic response (4) Conflicting results were also found in recent studies including measurement of arterial oxygen tension this can be due to small groups of patients (34) and/or a selection that involved a predominance of patients with haemoglobin concentrations and/or haematocrits within (5) or above (13 15 16) the normal range

The aim of the present study was to assess the relationship between haematologic adaptation and the degree of respiratory insufficiency as estimated by spirometry and measurement of gas tensions in the blood and bone marrow in a representative group of patients with chronic bronchitis and pulmonary insufficiency

METHODS AND MATERIAL

Dynamic spirometry was performed with a Bernstein spirometer as described by Berglund et al (2) and Birath et al (3) The mean values for normal persons of comparable sex age and height were obtained by these authors and Grimby and Söderholm (9)

Measurements of gas tensions (28) and pH were undertaken with a conventional electrode system (Radiometer Copenhagen) For zeroing the oxygen electrode a borax solution saturated with sodium sulphite was used This procedure did not cause any drift of the zero as previously suggested by Severinghaus (27) Blood gases were measured by double determinations immediately after sampling and at 38°C The accuracy of measurements to one decimal place is shown in Table I All tests

Table I *Accuracy in measurements of PO_2 and PCO_2 in arterial venous and bone marrow blood (mmHg) using double determinations*

	Double analyses (*n*)	Range	Mean	S D
PaO_2	54	44 0–100 0	66 01	0 78
$PaCO_2$	49	37 8– 81 0	60 39	0 80
PvO_2	52	16 0–62 5	33 46	0 71
$PvCO_2$	50	44 5– 98 0	70 41	1 20
PmO_2	52	33 5– 64 1	49 45	0 85
$PmCO_2$	39	37 9– 92 0	61 13	1 55

Table II *Cardiovascular complications in 82 patients with chronic bronchitis and pulmonary insufficiency*

Age (y)	No of pats	Dilatation of the heart	Persistent cardiac insufficiency	Arterial hypertension
<40	1	0	0	0
40–50	7	1	0	0
51–60	26	3	1	3
61–70	41	6	3	2
>70	7	2	2	1
Total	82	12	6	6

ere made on patients at rest Ten ml blood was taken m the cubital vein without stasis and 10 ml from the oral artery Bone marrow blood was drawn after ternal puncture using a short canula 1 ml was drawn for measurement of the oxygen tension (PmO_2) and 2 ml immediately afterwards for measurement of the carbon dioxide tension ($PmCO_2$) Heparin was used as anticoagulant For consecutive aspirations of bone marrow blood a difference in PmO_2 less than 2 mmHg was found in 16 out of 18 cases and of less than 5 mmHg in the others In 41 patients PmO_2 was measured from two points of puncture In 30 patients the difference was less than 4 mmHg and in 11 up to 8 mmHg The lower values were always found in the second sample

Arterial oxygen saturation as a percentage of the normal (%$SatO_2$) was calculated from the PaO_2 measurement with a correction for excess base as described by Severinghaus (26)

Haemoglobin concentration (Hbc) was measured as oxyhaemoglobin using cyanmethhaemoglobin as a standard (10 20) The haematocrit (Hct) determination was made by the Wintrope method as described by Ham (11) Plasma volume was measured with Evans blue as described by Tornberg (32) The total Hb mass (Hbt) erythrocyte volume (RCV) and blood volume (BV) were calculated from the plasma volume Hbc and corrected Hct values The measured Hct values were multiplied by a factor of 0 92 to correct for trapped plasma (8) and the difference between the body Hct and peripheral venous Hct levels (24) The patients expected normal values for BV were calculated from body weight using tables (22) while normal values for Hbt and RCV were calculated using a factor of 0 43 for the corrected normal Hct and 145 g/l for the normal Hbc The values found for Hbt RCV and BV were given as a percentage of predicted normal values (Hbt%pHbt RCV%pRCV BV%pBV)

The study was carried out in 1966–71 and included males admitted to the Out patient Clinic and the ward with chronic bronchitis (21) and persistent breathlessness for at least one year Only patients who had undergone thoracic surgery with marked thoracic deformities from other causes diagnosed malignant disorder or haemorrhage were excluded from the study Patients admitted because of transient aggravation were examined when their usual condition was judged to be restored In all 82 patients aged 39–76 were examined

RESULTS

Spirometric estimation was made on 78 patients In 75 (96%) the forced expiratory volume in the first second ($FEV_{1\,0}$) was 0 3–1 6 l and the forced vital capacity (FVC) 0 8–3 0 l For the total number there was a highly significant linear correlation between $FEV_{1\,0}$ and both FVC (r=0 844) and the maximum voluntary ventilation (r=0 911) The patients distribution according to $FEV_{1\,0}$ as percentages of predicted normal values for $FEV_{1\,0}$ ($FEV_{1\,0}$%p$FEV_{1\,0}$) and VC ($FEV_{1\,0}$%pVC) can be seen from Fig 1

The age distribution and the presence of dilatation of the heart established by X ray persistent cardiac insufficiency (pulmonary stasis peripheral oedema) and arterial hypertension (diastolic BP

Table III *Correlation coefficients for arterial hypoxia and haematologic parameters*

	Total series (n=82–81)		Arterial pH–venous pH≤0 04 (n=29)	
	PaO_2 (r)	%$SatO_2$ (r)	PaO_2 (r)	%$SatO_2$ (r)
Hbc	−0 654	−0 663	−0 771	−0 765
Hct	−0 712	−0 749	−0 731	−0 781
BV%pBV	−0 461	−0 533	−0 656	−0 650
Hbt%pHbt	−0 675	−0 740	−0 850	−0 853
RCV%pRCV	−0 723	−0 796	−0 854	−0 890

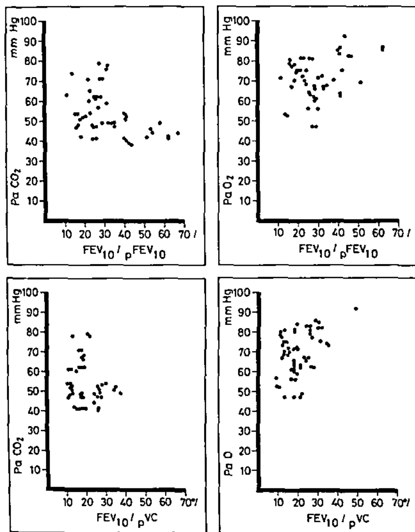


Fig 1 $PaCO_2$ and PaO_2 in relation to $FEV_{1.0}$ as a percentage of predicted normal values for $FEV_{1.0}$ ($FEV_{1.0}$ %p$FEV_{1.0}$) and VC ($FEV_{1.0}$ %pVC)

above 100 mmHg and/or systolic BP above the numerical value for the age +100) are shown in Table VI Among the 12 patients with cardiac dilatation four had persistent cardiac insufficiency One of these and three others had hypertension Among the remaining 70 patients persistent cardiac insufficiency was present in two and hypertension in two Four patients had been treated for pulmonary tuberculosis

The relationship between spirometric data and arterial gas tensions

With decreasing values for $FEV_{1.0}$%p$FEV_{1.0}$ and $FEV_{1.0}$%VC the scatter of $PaCO_2$ and PaO_2 values increased but with continuing normal arterial gas tensions in some patients Only in patients with values below 15 and 10% respectively was $PaCO_2$ abnormally high in all cases (Fig 1) For all the patients and for a subgroup of 33 patients with $FEV_{1.0}$%pVC≤20% and an arterial blood pH between 7 34 and 7 42 a negative linear correlation was found between $PaCO_2$ and PaO_2 with approximately the same regression equation and coefficient of correlation ($r=-0\ 6385$ $r=-0\ 6193$)

The relationship between cardiovascular complications and arterial gas tensions

Thirteen out of 14 patients with radiologically established dilatation of the heart and/or persistent cardiac insufficiency had a $PaCO_2$>60 and a PaO_2

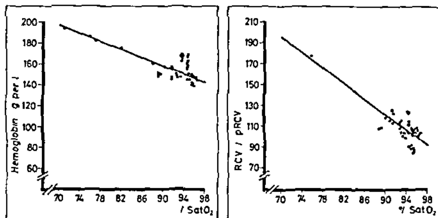


Fig 2 Relationship between arterial oxygen saturation corrected for excess base (*%SatO₂*) and Hb concentration and erythrocyte volume as a percentage of the predicted normal value (*RCV %pRCV*)

<70 mmHg These complications were demonstrated in all six patients with a PaO_2<50 mmHg and in five out of nine with a PaO_2 between 50 and 60 mmHg

The relationship between arterial hypoxia and capacity for intravascular oxygen transport

For the whole group of patients (PaO_2 44–100 mmHg) there was a correlation between the degree of arterial hypoxia and the values for Hbc Hct BV%pBV Hbt%pHbt and RCV%pRCV (Table III Fig 2) The calculated regression equation Hbc=329 861 − 1 901×%$SatO_2$ indicates a relation between %$SatO_2$ and Hbc which ensures an approximately constant oxygen content The pH of arterial blood was above 7 30 in all patients and between 7 34 and 7 46 in 75 For a subgroup with difference in the pH of arterial and cubital venous blood ≤0 04 there was the same correlation between arterial hypoxia and the haematologic parameters as for the patients as a whole (Table III) Twenty-one of these patients and all but one of the 22 with a difference in pH of arterial and venous blood ≥0 08 had PaO_2 values above 60 mmHg Only for the latter of these two subgroups was there no correlation between the degree of hypoxia and Hbc (Table IV)

Among 16 patients with radiologically established dilatation of the heart persistent cardiac insufficiency or hypertension 13 had pH values for arterial blood ≥7 34 and 12 had a difference in pH of arterial and venous blood ≤0 04 Differences ≥0 08 did not occur in this group Values for Hbc >175 g/l and for RCV%pRCV>130% were found in 11 and 12 respectively of these patients compared with three and nine patients respectively among the remaining 66 For both these subgroups there were negative linear correlations between PaO_2 and %$SatO_2$ on the one hand and values for Hbc Hct Hbt%pHbt and RCV%pRCV on the other ($2p$<0 01–0 001)

Table IV *Correlation coefficients for %SatO₂ and haematologic parameters in patients with differences between pH in arterial and venous blood ≥0 08 and in patients with differences ≤0 04 and PaO₂ above 60 mmHg*

	Arterial pH – venous pH					
	≥0 08			≤0 04		
	n	*r*	*2p*	*n*	*r*	*2p*
Hbc	22	−0 161	–	21	−0 508	0 05
Hct	22	−0 315	–	21	−0 429	0 1
BV%pBV	21	−0 588	0 05	21	−0 531	0 05
Hbt%pHbt	21	−0 501	0 05	21	−0 703	0 001
RCV%pRCV	21	−0 609	0 01	21	−0 712	0 001

The relationship between PaO₂ PmO₂ and haematologic parameters

In patients with a PaO_2 above 80 mmHg the PmO_2 varied between 70 and 34 mmHg When PaO_2 was below 60 mmHg PmO_2 was between 46 and 36 mmHg For all the patients and for subgroups comprising partly patients with differences in pH of arterial and venous blood ≤0 04 and partly patients with cardiovascular complications there was a linear correlation between PaO_2 and PmO (r= 0 4428–0 718) For the subgroup with differences in pH of arterial and venous blood ≥0 08 no correlation was found (r=0 1743)

There was a significant correlation between

PmO_2 and haematologic parameters for all patients and for the subgroup with little difference between the pH of arterial and venous blood but the correlation was less than that for PaO_2 and corresponding parameters ($p<0.05$)

DISCUSSION

The spirometric data are typical for patients with chronic bronchitis cooperating well (30) The upper limit for $FEV_{1.0}\%pFEV_{1.0}$ and $FEV_{1.0}\%pVC$ associated with hypercapnia is in agreement with previous findings (25 31) but the large scatter of PaO_2 and $PaCO_2$ values in patients with severe insufficiency judged by spirometry makes the latter unsuitable as the only means for assessing the degree of respiratory insufficiency As indicators of serious respiratory insufficiency evidence of cardiac dilatation and/or persistent cardiac insufficiency seems to be more reliable The lack of correlation between spirometric findings and arterial gas tensions can be explained by the fact that spirometric data predicate nothing about actual ventilation or pulmonary conditions which can influence the uptake of oxygen and elimination of carbon dioxide (35) Thus an accurate assessment of the degree of respiratory insufficiency in patients with chronic bronchitis and marked pulmonary insufficiency in a stable condition requires measurement of arterial gas tensions

As assessed from pH values obtained for arterial blood 93% of the patients were adapted to the abnormal conditions The correlation between arterial oxygen saturation and Hb concentration for the patients as a whole and for a selected subgroup corresponds to the correlation found in exminers by Chan (4) The increase in RCV%pRCV with falling PaO_2 values was a little steeper than in patients selected because of a high packed cell volume or hypercapnia (15 16) and examined with a similar technique (29 33) As the present findings agree with those in normal persons with high altitude hypoxia (5 34) it can be concluded that a majority of the present patients had obtained a normal haematologic adaptation to the abnormal conditions

In these patients the haematologic parameters were better correlated with PaO_2 than with PmO_2 In patients with a large difference in pH of arterial and venous blood PmO_2 values were often low This was probably due to the lack of correlation between arterial hypoxia and Hbc in this subgroup Thus nothing indicated that a decreased oxygen supply to the bone marrow is of significance for the increased erythrocyte and Hb production in patients with arterial hypoxia due to chronic bronchitis

From the relationship between hypoxia haematologic parameters and the occurrence of cardiac dilatation and/or persistent cardiac insufficiency it is understandable that the expected connection between arterial hypoxia and haematologic parameters is obtained with a high coefficient of correlation in groups selected because of high Hct values and/or hypercapnia (15 16) and that polycythaemia occurred far more frequently in patients with the severest forms of chronic cor pulmonale than in those without such cardiovascular complications (1) In groups with moderate to minimal hypoxia a better correlation can be obtained for Hbt than for Hbc (29 33)

Evidence of an increase in the circulating BV RCV and Hbt with or without a relatively smaller increase in Hbc could indicate that hypoxia brings about an increase of the vascular capacity Haematological adjustment to an increase in vascular capacity can ensure normal venous flow back to the heart despite changes in regional blood distribution and blood flow But only an increase in Hbc can compensate for a reduction in arterial oxygen saturation However no mechanism involved in oxygen transport can ensure values for PO_2 in tissues higher than PaO_2 Below a certain level stability cannot be maintained This can explain why all patients with a PaO_2 below 50 mmHg had persistent cardiac insufficiency and/or radiologically demonstrated cardiac dilatation and why not one patient of those studied had a PaO_2 below 44 mmHg or a PmO_2 below 34 mmHg

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Peripheral Circulation Particularly Heat Regulation Reactions, in Patients with Amyloidosis and Polyneuropathy

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ABSTRACT As patients with amyloidosis and polyneuropathy often have signs and symptoms of circulatory disturbances in the extremities, especially the legs we have examined such patients and controls with oscillometry and digital pulse plethysmography in order to estimate the occurrence of any arterial circulatory insufficiency No signs of significant obliterative arterial changes were found Skin temperature was also determined in fingers and toes during body-cooling and at subsequent indirect heating At low environmental temperature the skin temperature was higher in patients than in controls In a few patients there was almost no decrease in skin temperature despite a long period of cooling and a low rectal temperature Indirect heating elicited a marked increase in the skin temperature of the toes and fingers of the controls In most patients this reaction was completely absent in the toes and absent or reduced in the fingers These deviations can be explained by nerve damage caused by amyloid deposition in the nerves Amyloid deposits in the walls of small blood vessels may be an additional factor Maximum blood flow in the anterior tibial muscle after combined ischemia and exercise investigated with radioactive xenon was reduced in half of the patients

In primary amyloidosis with polyneuropathy sensory and motor nerve disturbances usually start distally in the extremities The form of the condition which occurs in Northern Sweden (1 6) is characterized by the symptoms arising first in the legs and being most pronounced there A common and early symptom is a troublesome coldness distally in the extremities particularly in the feet (1) Several patients have reported an increased sensitivity to cold and a persistent painful feeling of coldness after being cooled The sensation of chilliness usually declines successively as the illness continues at the same time as sensibility is completely lost There are often trophic changes such as dry thin and lifeless skin and trophic ulcers Before the diagnosis of amyloidosis neuropathy was established the chilliness and susceptibility to cold were often interpreted as expressions of insufficiency of the arterial circulation in these patients This led to an angiographic investigation of the lumbar aorta and of the arteries in the lower limbs in three patients (2) The investigation revealed a delayed contrast filling of the peripheral arteries but no obliterative processes were found

The clinical manifestations above have prompted this study of the occurrence of any arterial circulatory insufficiency in the lower extremities of patients with amyloidosis and polyneuropathy combined with an investigation of the peripheral circulation distally in the extremities especially temperature regulation reactions of the blood vessels As far as is known such an investigation has not previously been performed

MATERIAL

The study comprised 8 male patients admitted to the Department of Medicine University Hospital Umeå They had symptoms and signs of polyneuropathy (Table 1) Amyloidosis was confirmed by histopathological investigation of biopsy material Each patient was designated with a capital letter In four patients the condition was found to be familial designated with an addi

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Table IV *Skin temperature (°C) on 2nd fingers and toes and difference from room temperature and rectal temperature during body cooling in 8 controls and in 8 patients with amyloidosis and polyneuropathy*

	Room	Fingers	Toes	Difference Fingers–room	Toes–room	Rectum
Controls						
Mean	16 1	17 1	17 0	1 0	0 9	36 9
S D	1 2	2 8	1 1	2 5	1 2	0 4
Patients						
Mean	17 9	21 6	23 2	3 7	5 3	35 7
S D	0 8	5 5	4 9	4 9	4 5	0 8

same time the difference between the skin temperature of the toes and the room temperature was significantly larger ($p<0.05$) in the patients these differences occurred even though the rectal temperature tended to be lower in the patients (Table IV) In the *fingers* the tendency was the same as in the toes but it was not statistically significant

In patient B 3 the skin temperature at cooling

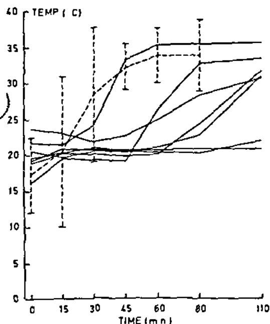


Fig 1 Skin temperature in the fingers during body cooling and indirect heating in 7 patients with amyloidosis (—) and mean values ±2 S D in 8 controls ( ) Heating started at time 0

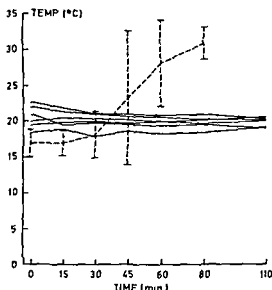


Fig 2 Skin temperature in the toes during body-cooling and indirect heating in 6 patients with amyloidosis (—) and mean values ±2 S D in 8 controls (--) Heating started at time 0

was 33 7°C in the fingers and 31 8°C in the toes The corresponding values for patient L were 23 8°C and 29 8°C This was so even though the cooling time was extended for both these patients The cooling procedure had to be terminated when they began to shiver violently The rectal temperature was then 34 1°C and 35 8°C respectively

Reaction to indirect heating In the controls the skin temperature increased in the fingers to 32 8°C ±2 5 and in the toes to 30 9°C±1 1 during indirect heating The reaction to heating was not investigated in patient B 3 who had no decrease in skin temperature upon cooling In one patient (J) there was an increase in the temperature of the *fingers* which agreed with that found in the controls The other 6 patients differed significantly from the controls having either no increase at all in the temperature or a much slower increase than the controls (Fig 1)

For patient L the skin temperature of the *toes* remained unaltered (29 6°C) during the heating period The results of heating in the other 6 patients are shown in Fig 2 Although the patients rectal temperature at the end of the indirect heating period did not differ from that of the controls (37 2°C±0 5 and 36 9°C±0 4 respectively) the skin temperature of the toes did not increase in any of these 6 patients within a period of 110 min

DISCUSSION

Regarding the examinations performed to estimate the occurrence of any arterial circulatory insufficiency in the lower extremities oscillometry showed no significant difference between the patients the controls and a group of younger subjects who were investigated in the laboratory (unpublished data) This indicates that there were no substantial obliterative changes in the larger and medium large arteries of the patients examined

Digital pulse plethysmography showed IT and CT values which did not differ significantly between the two groups For both controls and patients the individual IT and CT values were well within the accepted normal limits (18) This indicates that substantial obliterative arterial changes were not present in the small digital arteries either (7) Furthermore the normal values for CT speak against a reduced arterial elasticity (18)

PT for the individual patients was well within the accepted normal limits (18) Six patients however had longer PT in fingers and/or toes than the controls mean +2 S D This relatively long PT and the absence of dichrotism in the pulse curve of fingers and/or toes in 5 patients can be explained by changed physical properties of the blood vessel wall Changes in the elasticity of the larger arteries may also have contributed to the absence of dichrotism (13)

The maximum blood flow in the anterior tibial muscle determined by radioactive xenon clearance in association with reactive hyperemia after combined ischemia and muscular exercise did not differ significantly between patients and controls The distribution of the control sample did not differ from that of the patient sample according to the *F* test although it was small Four patients had quite a normal clearance compared to accepted normal values (12) Two patients however were judged to have a very low clearance and 2 a moderately low Some patients had muscular atrophy and a reduced ability to perform muscular exercise Exertion in the form of foot movements can therefore have been a relatively weak stimulus for hyperemia in these cases The duration of ischemia was however probably sufficient to stimulate the arterioles to their maximum dilatory extent (17)

During general body cooling the skin temperature was higher and the difference between skin and environmental temperature was larger in the patients than in the controls especially in the toes although the rectal temperature tended to be lower This difference in skin temperature between the two groups at cooling was interpreted as an expression of decreased vasoconstriction in the patients It can be due to *a)* a reduction of impulses in the adrenergic vasomotor nerves *b)* a reduced reactive ability of the blood vessels *c)* a combination of these two factors The abnormal pattern was particularly evident in 2 patients (B 3 and L) At cooling they had a reaction almost identical with that of sympathectomized subjects (15)

It seems likely that sympathetic denervation more or less pronounced was present in these patients with amyloidosis If the denervation had been complete all the patients should have had an initially high skin temperature almost unaffected by the body-cooling and then also by the indirect heating procedure (15)

Indirect heating induced a marked increase in the skin temperature of both the toes and the fingers of the controls This reaction was completely absent in the toes of the patients examined and absent or reduced in the fingers of 6 of the 7 patients investigated This decreased ability to reflex vasodilatation can also be due to partial sympathetic denervation In spite of nerve damage with reduction of nerve impulses there may still be an adrenergic influence The reason why it persists on skin blood vessels could be that the normal reuptake of the released adrenergic transmittor substance norepinephrine into the nerve endings (8) is reduced due to the nerve damage Such a mechanism has been considered to occur also in diabetic subjects with peripheral neuropathy in whom a similar vascular response has been described (14)

Histopathological examination has shown deposits of amyloid substance to be very extensive in the peripheral nervous system including the autonomic (11) There is accordingly pathoanatomical evidence of nerve damage in this disease Amyloid deposition is also found in the walls of various blood vessels including the small ones in the skin (11) It is therefore conceivable that amyloid deposits in the walls of the small blood vessels may contribute to the vasomotor abnormalities found in the skin

The reduced ability for reactive hyperemia in skeletal musculature demonstrated in some of he patients is no doubt due in particular to the affection of the blood vessels (9) Similar disturb-

ances have been reported in patients with another form of systemic amyloidosis in whom amyloid vascular infiltration was pronounced according to findings at muscular biopsy (17) Amyloid involvement of the blood vessels of the skeletal musculature was found in our patients too (11)

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Skin Lesions of the Legs and Feet and Skeletal Lesions of the Feet in Familial Amyloidosis with Polyneuropathy

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ABSTRACT Twenty one patients with familial amyloidosis and polyneuropathy have been examined for the presence of skin lesions localized to the lower legs and feet The lesions were classified as atrophic skin lesions hypertrophic scar like skin lesions, rubeosis plantarum, spontaneous blisters, necrotic skin lesions, yellow nails, traumatic skin lesions purpura and abundant pigmented small non atrophic spots Skeletal destructions in the feet were also demonstrated In many respects these lesions are similar to those of long standing diabetes mellitus I studied the cutaneous reactions to local thermal trauma with heat and cold to the legs and forearms in 11 patients Petechiae were observed within the area of traumatization with either heat or cold more often in patients than in controls Four of the 11 patients developed atrophic circumscribed skin lesions at the site of traumatization

Lesions of the lower extremities of diabetics especially skin lesions have been studied for 15 years at the Department of Medicine University of Umeå In 1964 Melin described an atrophic circumscribed skin lesion in the lower extremities of diabetics (18) These skin lesions common in diabetics are now called dermopathia diabetica (14) I have described cutaneous erythema with or without necrosis on the lower extremities especially in elderly diabetics (14 15)

Familial amyloidosis with polyneuropathy was first reported by Andrade in Portugal (7) and has also been reported from our department (1–6 12) I have observed that these patients often have skin lesions similar to those of diabetics Skin changes in familial amyloidosis with polyneuropathy have received little attention Andrade (7) mentioned perforating trophic ulcers and Andersson and Bjerle (2) reported trophic changes cutaneous ulcerations and peripheral reddish colouring of the extremities A more detailed study of the various skin lesions in patients with this type of amyloidosis is therefore desirable

I have found an altered reaction to thermal traumatization of the skin of the extremities of patients with long standing juvenile diabetes and elderly diabetics (15) There was among other things an increased number of petechiae within the area of traumatization The possible reasons for this altered reaction were discussed In the above mentioned groups of diabetics there are changes in the walls of the small vessels and often polyneuropathy Patients with familial amyloidosis generally have pronounced polyneuropathy and amyloid deposits in the small vessels (5 12) It is therefore of interest to compare the reaction to thermal traumatization in non-diabetic patients with amyloidosis to that of diabetics

MATERIAL AND METHODS

The material consisted of 21 patients 13 men and 8 women consecutively studied and examined during the last year most of them at the Department of Medicine University of Umeå but a few in their homes The mean age was 55 years for men and 54 for women (range 28–83) The diagnosis of amyloidosis had earlier been established by light microscopical examination of biopsy specimens (5)

The peripheral neuropathy was graded on clinical manifestations according to a scale described by Andersson and Blom (3) Legs + = slight (1 case) + + = moderate (8 cases) + + + = pronounced (12 cases) Arms 0 = no clinical signs (3 cases) + = slight (7 cases) + + = moderate (11 cases) + + + = pronounced (no cases)

Table I *Frequency of lesions observed on the lower extremities of 21 patients with familial amyloidosis and polyneuropathy*

The denominator in the fractional numbers indicates the number of individuals investigated and the numerator the number of these individuals with the particular skin changes indicated in the table heading

	Age group (y)	
	<50	≥50
Atrophic skin lesions	6/8	11/13
Hypertrophic scar like lesions	4/8	4/13
Rubeosis plantarum	4/8	6/13
Spontaneous blisters	1/8	1/13
Necrotic skin lesions	1/8	3/13
Yellow nails	1/8	5/13
Traumatic skin lesions	2/8	2/13
Edema of the legs	1/8	5/13
Skeletal destructions in the feet	1/8	2/13

Electromyography (EMG) and measurement of motor conduction velocity (MCV) were performed on the legs of 17 of the patients Only one patient indicated above as having slight polyneuropathy in the legs presented with normal findings EMG and measurement of MCV on the upper extremities of 15 patients revealed normal findings in only three None of these patients had signs of arterial insufficiency Two patients both with cardiac pacemakers had long standing cardiac decompensation None had open diabetes oral glucose tests were performed in 17 patients and were all normal

Thermal traumatization of the skin of the legs and forearms was performed in 11 patients four men and seven women and in 25 controls from a previous study (14) Three of the patients were below 50 years of age 43) and eight above 50 years (mean 61) Localization with heat was performed at 60 and 55°C an electrically heated brass rod and with cold using a pencil of solid carbon dioxide as described previously (15) For both heat and cold the exposure time was 5 sec

When possible the traumatized areas have been observed after 1 7 14 21 60–80 120–140 and 200–220 days When skin changes existed they were photographed in colour All patients showed a positive attitude to the investigation Experience demonstrated that there were no risks involved Differences between groups were tested using Fisher s exact probability test $p<0.05$ was chosen as the level of statistical significance

RESULTS

Clinical description

More or less well defined skin lesions were found on the lower extremities of all except one of the patients whereas only one patient had skin lesions on the upper extremities a single blister on the dorsum of one finger The observed skin lesions were classified as shown in Table I

Atrophic skin lesions (Fig 1) Most of the patients had multiple skin lesions which appeared as depressions in the skin surface They varied in size but were usually less than 10 mm in diameter often pigmented If they were depigmented they often had a smooth and shiny appearance There were often telangiectatic formations within the atrophic area The atrophic skin lesions were either isolated or occurred in groups often in a linear pattern along the bony parts of the legs only seldom on the feet These skin lesions were asymptomatic often round and circumscribed indistinguishable from the well known atrophic circumscribed skin lesions in diabetics (18) but appeared sometimes irregularly sometimes confluently and sometimes in connection with the hypertrophic scar like lesions described below The patients were often not aware of the existence or origin of these skin lesions The

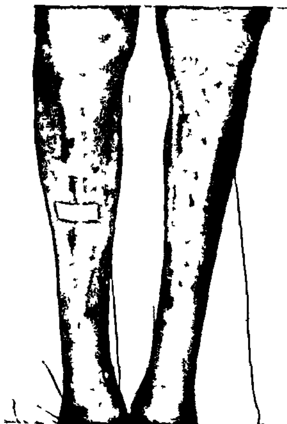


Fig 1 Multiple atrophic skin lesions and hypertrophic scar like lesions on the ventral aspects of the lower legs of a 66-year-old male patient

appearance of the initial stages of these skin lesions are not known with sureness but they are probably encrusted ulcers involving only the superficial layers of the skin and surrounded by a slightly reddened border

Hypertrophic scar like skin lesions A type of skin lesion consisting of smooth red slightly elevated homogeneous areas up to several cm in diameter and often with irregular borders was often observed on the lower extremities of these patients Telangiectatic formations were often seen within these lesions Most patients were not aware of the origin of these asymptomatic lesions but a few assigned them to a certain trauma as far as 2 years back The appearance of the scars was often resembling scars in normal men The histopathological finding of the lesion in one patient was compatible with that of scar tissue Amyloid deposits and abundant telangiectatically dilated vessels were also seen

Rubeosis plantarum Intense reddening of the soles of the feet was seen in 10 patients 9 of whom also had red toes

Spontaneous blisters One patient suddenly developed multiple tense asymptomatic bullae over the dorsum and the sole of the left foot The largest bulla was approximately 5 cm in diameter Clear contents could be seen through the transparent walls There was no peripheral erythema They were painless and apparently not associated with trauma In another patient a similar bulla suddenly developed on the extensor side of one finger

Necrotic skin lesions One patient had deep perforating partly black gangrenes about 6 cm in diameter on both heels and edema of both legs There were narrow only slightly erythematous zones surrounding the gangrenes Another patient had a spontaneous perforating ulcus of so-called mal perforant type under the right great toe Two of the patients had several black nail beds apparently spontaneously

Yellow nails Smooth and somewhat thickened yellow toe nails were seen in six patients those of all 21 who had the disease in the most pronounced state As a rule all toe nails were affected The colour was sometimes seen or was most pronounced only on the distal part of the nails Five of these six patients had pronounced edema of the lower extremities of long duration and only one was without obvious edema

Traumatic skin lesions Two patients developed third degree burns on their feet while bathing them as they did not feel that the water was too hot One of them returned a few months later with new third degree burns caused by sleeping on an electrically heated pad Two other patients each had a large blister on the greater part of the sole of one foot most likely caused by walking One of them had earlier had a rather deep friction sore on one foot from which she experienced no pain

Edema of the legs Six patients had pronounced edema of the feet and/or legs Two of them had cardiac disease and none had nephropathy

Skeletal destructions in the feet Rather pronounced skeletal destructions were demonstrated roentgenographically in one patient They were localized to the metatarsophalangeal region of dig III of the left foot There had never previously been any necrosis of the skin in this region but approximately two years earlier the patient had had pain and swelling of unknown cause in that foot A biopsy revealed so-called chronic unspecific inflammation and no amyloid deposits One patient had several years earlier been investigated roentgenographically in connection with pain and swelling of the right foot Pronounced destructions of the calcaneus adjacent to the talus were demonstrated Another patient had destructions in the metatarsophalangeal region of the left great toe where skin lesion had never existed

Purpura and abundant small pigmented non atrophic spots Apparently spontaneous petechiae were found on the lower legs of two patients Abundant small pigmented non atrophic spots were found on the lower extremities of three patients two of whom had pronounced edema of the legs of long duration The information concerning the occurrence of these latter skin lesions is incomplete because in the beginning of this investigation we were not aware of the relationship between these skin lesions and amyloidosis with polyneuropathy

Cutaneous reactions to local thermal trauma

The majority of the subjects investigated developed erythema and blisters at the sites of thermal trauma and none of them developed necrosis of the skin Some of those investigated developed small hemorrhages (petechiae) in the area of traumatization Four patients eventually developed atrophic circumscribed skin lesions at the site of traumatization

Table II *Frequency of petechiae in the area of experimental traumatization at some time during the observation period in 11 patients with familial amyloidosis and polyneuropathy and in 25 controls*

No of individuals indicated as in Table I

	Amyloidosis		Controls	
Age group (y)	<50	≥50	<50	≥50
60°C				
Legs	3/3	8/8	0/19	4/6
Forearms	1/3	6/8	0/19	0/6
55°C				
Legs	0/3	4/8	0/19	0/6
Forearms	0/3	0/8	0/19	0/6
Cold				
Legs	3/3	8/8	0/17	4/6
Forearms	2/3	3/8	0/17	0/6

Petechiae were often observed in the areas traumatized with either heat or cold both in patients and controls (Table II) They were often first observed seven days after traumatization and appeared later than blisters with approximately the same incidence at the sites traumatized with heat at 60°C as at those traumatized with cold They were seen less often at sites traumatized with heat at 55°C

Petechiae occurred more often and were more abundant on the legs than on the forearms and were observed more often in patients with amyloidosis than in controls In the patients they occurred after traumatization with heat at 60 and 55 C In the petechiae were observed only in those than 50 years and only on the legs after traumatization with heat at 60°C and cold but not with heat at 55°C Petechiae in controls were always solitary In patients they were more abundant often confluent and significantly more frequent in amyloidosis patients younger than 50 years than in controls of the same age (legs heat 60°C $p<0.001$ forearms cold $p<0.07$) No significant difference was found between patients and controls older than 50 years in the occurrence of petechiae on the legs while the difference in the findings on the forearms was significant (heat 60°C $p<0.01$)

Atrophic circumscribed skin lesions (Fig 2) Nine of the 11 patients in whom thermal traumatization was performed had atrophic skin lesions on the legs before the application of thermal trauma After thermal traumatization with heat at 60°C four of these 11 patients developed atrophic circumscribed skin lesions as a result of the experimental trauma three of the same four patients also after traumatization with cold The interval between traumatization and the appearance of these skin lesions was three months or more The lesions were pigmented and very much like the skin lesions they already had on the lower extremities None of the controls developed late skin lesions as a result of the traumatization

There were no obvious qualitative differences between the skin reactions either to the local application of heat or to cold

DISCUSSION

With regard to their appearance the atrophic skin lesions in patients with familial amyloidosis and polyneuropathy often could not be distinguished

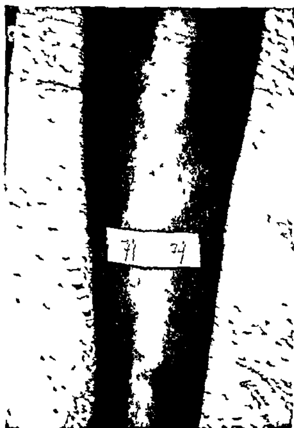


Fig 2 Atrophic circumscribed skin lesion on the area of traumatization 4 months after application of heat at 60°C on the left leg of a 53 year-old female patient The spot above the tape is the lesion

from the atrophic circumscribed skin lesions seen in dermopathia diabetica (14 18) Telangiectatic for mations were sometimes seen within the atrophic areas as mentioned above In this connection it is to be noted that in a microangiographic study and in disappearance studies with locally injected isotopes (I^{131} and Na^{24}) the diabetic atrophic circumscribed skin lesions showed an increased vascularity as compared to the adjacent intact skin (18)

The resemblance between rubeosis plantarum in patients with amyloidosis and rubeosis plantarum in diabetics is striking the latter mostly seen in elderly patients (14 17) Obvious redness of the toes can be seen in both groups of patients

Spontaneous blisters have also been described in diabetics and termed bullosis diabeticorum (8 13 19) In 1971 Kurwa et al (13) reviewed 28 diabetic patients with spontaneous bulla formation de scribed in the literature including 3 of their own cases In diabetics these lesions are mainly localized to the feet and less often to the upper extremities

The necrotic skin lesions including the phe nomenon of black nail beds resemble certain lesions in diabetics i e distal gangrene and mal perforant plantaire with the exception that the red ness of the border zones to intact skin is less pro nounced in patients with amyloidosis

In diabetics (14) as well as patients with amyloi dosis skeletal destructions in the feet beneath appar ently intact skin may be demonstrated These skeletal lesions in patients with familial amyloidosis and polyneuropathy are apparently different from amyloid joint disease in connection with for exam ple myeloma (24) In amyloid joint disease which is uncommon histopathological investigation dem onstrated amyloid deposits and the skeletal X rays were normal

Purpura and abundant small pigmented non atrophic spots on the lower extremities occur in patients with amyloidosis as well as in diabetics (16)

Six of the present 21 patients with amyloidosis had yellow nails on the feet This symptom has earlier been described in patients with peripheral vascular disease (10 20) and considered to be due to impaired peripheral blood supply Yellow nails have also been described in connection with pri mary lymphedema (11 21) cardiac decompensa tion (22) and diabetes (16)

Purpura and abundant small pigmented non atrophic spots and yellow nails localized to the lower extremities often occur in patients with amy loidosis as well as in patients with juvenile diabetes of long duration or in elderly diabetics (16) Both in patients with amyloidosis and in diabetics with these lesions there is often edema of the legs Only two of the six patients in this study with edema of the legs had clinical symptoms of cardiac disease and none had nephropathy Pronounced muscular *atrophy particularly in the lower legs in patients* with amyloidosis might be a cause of the edema of the legs The muscular atrophy ought to impair the venous return due to decreased function of the so-called muscle pump

The patients with amyloidosis generally exhibited petechiae within the area of thermal traumatization In a previous investigation diabetics were compared with controls (15) In patients with long standing juvenile diabetes and in elderly diabetics there was a reaction similar to that seen in the patients with amyloidosis Petechiae on the forearms were how ever less common in diabetics compared with pa tients with amyloidosis From a physical point of view the thermal traumatization of the skin was identical in the patients with amyloidosis and the controls However this does not imply that they were biologically identical Concerning this ques tion refer to the discussion in the previous paper on diabetics (15)

The polyneuropathy of patients with amyloidosis is pronounced both in the lower and the upper ex tremities By recording skin temperatures Anders son and Bjerle (2) demonstrated that patients with amyloidosis differ from controls by a decreased capacity to vary the blood perfusion distally in the extremities As mentioned in the introduction there are amyloid deposits in the walls of the small blood vessels of these patients Details concerning these amyloid deposits are not known The altered reac tion to local thermal traumatization in patients with amyloidosis and in diabetics can be explained by an impaired supply of oxygen to the cells of the tissue and/or transport of metabolites from the tissue The occurrence of edema may further impair the pas sage of oxygen and metabolites by interposition or by bringing about a compression of the small blood vessels

Diabetics with atrophic circumscribed skin le sions (dermopathia diabetica Melin) after approxi mately three months often developed atrophic

circumscribed skin lesions at the site of traumatization In many of these patients the area of traumatization was surrounded by an intensely reddened border In a corresponding way and after the same length of time the patients with amyloidosis often developed atrophic circumscribed skin lesions at the site of traumatization An intensely reddened border surrounding the area of traumatization was never seen in these patients

Necrotic and traumatic skin lesions are common in patients with amyloidosis and polyneuropathy and might be due not only to the impaired sensibility but also to an altered reaction to traumatization

The necrotic and traumatic skin lesions healed in all patients They were treated with ordinary adhesive tape (9 23) and elimination of edema The described skin lesions most often have a rather characteristic appearance Their presence should give rise to the suspicion of familial amyloidosis with polyneuropathy

ACKNOWLEDGEMENT

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Purpura, Pigmentation and Yellow Nails of the Lower Extremities in Diabetics

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ABSTRACT This article describes purpura and pigmentations of the lower extremities as well as yellow nails mainly in elderly diabetics but also in persons not known to have diabetes When the latter were compared to controls, it appeared that their glucose tolerance was altered in a diabetic direction Precipitating factors could generally be established for these lesions predominantly cardiac decompensation with edema of the legs, and were more common in patients not known to have open diabetes than in patients with open diabetes Petechiae were transformed into small pigmented non atrophic spots Petechiae and pigmented spots were often seen simultaneously In a few patients small, pigmented, non atrophic spots were seen as pronounced brown black pigmentation on the lower legs and feet In a number of patients with open diabetes or diabetic glucose tolerance, erysipelas with purpura within the area of erysipelas was observed on the lower extremities Patients with no purpura within the area of erysipelas generally had normal glucose tolerance The pathogenesis of these lesions is discussed Atrophic circumscribed skin lesions (Melin), cutaneous erythema, with or without necrosis purpura, pigmentation, red toes as well as rubeosis plantarum, yellow nails and neuropathy are often seen simultaneously on the lower extremities of patients with open diabetes as well as of those without open diabetes but with diabetic glucose tolerance

Diabetic lesions especially skin lesions on the lower extremities have been studied at the Department of Medicine University of Umeå for 15 years In 1964 Melin (14) described an atrophic circumscribed skin lesion localized to the lower extremities of diabetics dermopathia diabetica (8)

I have earlier described cutaneous erythema with or without necrosis of the legs and feet especially in elderly diabetics (8 9) Three other lesions of the lower extremities apparently typical of diabetes purpura pigmentation and yellow nails have also been observed at our department and will be described in this article A close study has been made of them including an attempt to identify possible precipitating factors

It is well known that diabetics have increased capillary fragility which was probably first described by Hanum (4) In a survey article (1) diabetes is mentioned as a possible cause of purpura but no information about the localization of the purpura is given To our knowledge no systematic studies or case reports have yet been published Cardiac decompensation has also been mentioned as a possible cause of purpura (3) but again no systematic studies have been reported and no mention has been made of a possible connection with diabetes

Yellow nails have earlier been described in patients with peripheral vascular disease (5 15) and have been considered a symptom of impaired peripheral blood supply Yellow nails have also been described in connection with primary lymphedema (6 16) cardiac decompensation (17) and familial amyloidosis with polyneuropathy (10) To our knowledge a connection with diabetes has not been described earlier

DEFINITIONS MATERIAL AND METHODS

In this study purpura is defined as the presence of numerous petechiae or somewhat larger cutaneous hemorrhages localized to the legs and/or feet Pigmentation refers to a diffuse spread of small pigmented non atrophic spots often confluent to larger and rather uniform areas and localized to the legs and/or feet Yellow nails refer to

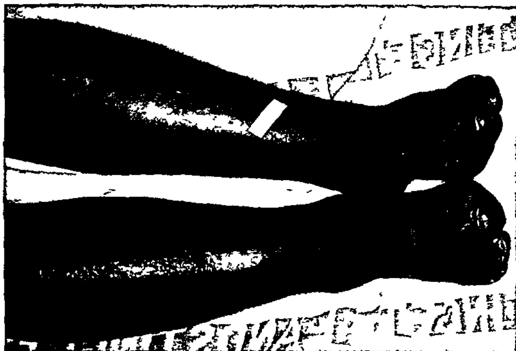


Fig 3 Male 75 years old diabetic oral glucose tolerance curve Severe and recurrent cardiac decompensation during the last 2½ years now with edema of the legs Pronounced brown black pigmentation of the legs and feet Erythematous dorsal surfaces of the feet with multiple petechiae Cyanosis of the toes
The patients in Figs 2 and 3 had been registered by the author about 2½ years earlier At that time *they also had pigmentation of the legs and feet but not so pronounced*



Fig 4 Male 45 years old diabetes of 35 years duration Edema of the feet of unknown cause Yellow toe nails

open diabetes and 0/9 for the patients not known to have diabetes The difference is significant ($p<0.01$)

Purpura and erysipelas localized to the legs and/or feet Purpura was observed within the area of erysipelas in all patients with open diabetes and in three of the four patients with diabetic glucose tolerance tests but was not observed in the patients with normal glucose tolerance tests (Table III) In none of these latter patients did the value of the glucose tolerance test exceed the 95% level of confidence of the mean of the controls In 12 of the 13 patients the affected leg was swollen Only two had cardiac decompensation ten had ulcers or fissures of the skin adjacent to the reddened area

DISCUSSION

The three lesions studied purpura pigmentation and yellow nails were most often observed in elderly patients with open diabetes and also in patients not known to have diabetes However comparison between the glucose tolerance test values in a group of the latter and in a control group showed a clear alteration in the diabetic direction Thus these skin lesions as well as atrophic circumscribed skin lesions in the lower extremities (Melin) and cutaneous erythema with or without necrosis localized to the legs and feet (8) are closely connected with diabetes With regard to purpura pigmentation or yellow nails both in patients with and without open diabetes precipitating factors most often cardiac decompensation with edema of the legs could generally be established This was also true for cutaneous erythema with or without necrosis (8)

As mentioned above the petechiae were transformed into small pigmented non atrophic spots Petechiae and pigmentation were often seen simultaneously and they were precipitated by the same factors These pigmented non atrophic spots are certainly sequelae after earlier purpuric lesions

In an earlier investigation (8) it was suggested that cutaneous erythema with or without necrosis is due to an altered reaction to certain precipitating factors such as cardiac decompensation This altered reaction may be released by a decreased blood flow through the distal parts of the lower extremities In a study of cutaneous reactions to local thermal trauma an altered reaction as compared to controls was demonstrated particularly for patients with maturity-onset diabetes and patients with juvenile diabetes of long duration (9) An increased number of petechiae was observed within the area of traumatization In an experimental study of alloxan diabetic rats we have demonstrated that the presence or absence of diabetes of long duration was of decisive importance to the cutaneous reaction to local thermal traumatization (11) Patients with familial amyloidosis and polyneuropathy showed a mode of cutaneous reaction to local thermal traumatization similar to that in the above mentioned diabetic patients The patients with amyloidosis were not diabetic (10) I suggested that the altered reaction in diabetics as well as in patients with amyloidosis is due to impaired transport of oxygen from the blood in the capillaries to the cells of the tissue and/or transport of metabolites from the tissue (9 10) Purpura pigmentation and yellow nails in diabetics can be explained by the same mechanism Precipitating factors for cutaneous erythema with or without necrosis were more common in patients not known to have diabetes than in patients with open diabetes (8) A similar difference between patients with and without known diabetes was also observed in the present study of purpura pigmentation and yellow nails

Pronounced brown-black pigmentations of the legs and feet of three patients were also described This pigmentation is regarded as a pronounced state of small pigmented non atrophic spots on the lower extremities

An account is also given of 13 patients with erysipelas on the lower extremities (Table III) Many of them—each with open diabetes or a clearly diabetic glucose tolerance—had purpura within the area of erysipelas Thus it seems that erysipelas can cause purpura in diabetic patients Purpura within the area of erysipelas has been described earlier (18) but information as to the possible concomitant presence of diabetes is lacking

Purpura especially localized to the lower extremities has earlier been given different names for example the purpura of Schamberg Gougerot and Blum or Majochi (7) Increased capillary fragility is said to characterize these conditions Information as to a possible relationship to diabetes is lacking

The diagnosis of diabetes in patients without glucosuria especially in the elderly can very often be made with a great certainty only by inspection of the lower extremities Rubeosis plantarum (8 13) is

Table I *Results of biopsies from different sites in 146 patients*

D=detected ND=not detected

Site of biopsy	No of biopsies	Suitable material obtained	Granulomas D	Granulomas ND
Scalene fat pad	140	99	51	48
Peripheral lymph node	2	2	1	1
Mediastinal lymph node	1	1	1	0
Liver	71	70	30	40
Salivary gland	2	2	2	0
Tonsils	4	4	0	4
Muscle	2	2	1	1
Skin	2	2	0	2
	224	*182*	*86*	*96*

cal Department TA Rigshospitalet with the diagnoses of sarcoidosis and/or BHL and/or pulmonary infiltrates roentgenologically suspected to be of sarcoid origin Criteria for selection were

1) The direct cause of the admission had to be the result of a routine chest X ray All the patients included were not known to suffer from any major disease before the X ray and almost all of them considered themselves to be in good health Through interrogation and examination upon admission 50 of the 146 patients turned out to have minor complaints and physical signs 96 had no complaints or physical signs at all In the majority of cases the complaints were sneezing and coughing (47 pats) and only a few patients had complaints such as chest pain (15 pats) and shortness of breath during exercise (9 pats) It is noteworthy that very few patients had any physical signs 8 had fever 9 palpable peripheral lymph nodes only one had erythema nodosum and one had petechia Thirty-eight patients were excluded either because of more severe ,mptoms leading to the present admission or because of a , examination that they were known to have prior to the admission

2) The patients selected had to have at least one organ *done This criterion caused 7 patients to be excluded*

Upon further interrogation during the admission 12 of the 146 patients turned out to have been examined earlier and to have been diagnosed as having one of the above mentioned diseases All except one were draftees 3 of *them had even had scalene fat pad biopsy performed and* in two cases lymph nodes containing granulomas had been obtained Most of them had recently i e within a few months been diagnosed as BHL at a chest clinic but some had been followed for 1–5 years Still they were enrolled in the army without this fact being noticed before the present admission Since these 12 patients all fulfilled the above mentioned criteria we found no reason for excluding them

Of the 146 patients selected 131 were young male draftees and 15 either officers or other kinds of military personel 142 were between 16 and 30 years and 4 between *31 and 50 years*

At the time of the study Medical Department TA Righshospitalet mainly functioned as a military hospital and therefore the patient material consists exclusively of men

METHODS

All the patients had at least one chest X ray performed 116 also had a tomography of the hilar region A follow up X ray was made in 36 of the patients within one year after the admission The others were referred to local chest clinics for follow up examination

As mentioned all patients had at least one biopsy performed 74 had two or more biopsies Altogether 224 biopsies were done in the 146 patients as shown in Table I Scalene fat pad biopsy was performed in 140 patients In most of the cases the biopsy was done as described by Daniels (5) i e the surgeon performed a dissection to the paratracheal fat tissue and removed a sample of this for histological examination In a few cases a macro lymph node was present in the region and was of course removed for histological examination During the first 4–5 years of the 10 year period the scalene fat pad biopsies were done in local anaesthesia in different surgical departments with no special experience of this biopsy procedure (general surgery (GS) group) In the last 5–6 years the biopsies were done in general anaesthesia in a head and neck surgical department specially trained in this biopsy technique (specially trained surgery (STS) group)

Liver biopsy a m Menghini (25) was performed in 71 patients 10 had other biopsies 13 in all from different organs and tissues (*Table I*)

An ophthalmologist examined 73 patients Routine blood analysis and determinations of serum creatinine and serum calcium were carried out in nearly all patients Serum electrophoresis and liver function tests were done as shown in Table VII

*Various serological reactions were tested in some pa*tients but only the toxoplasmosis complement fixation reactions are considered of importance in this connection

Gastric washings and/or sputum examinations for tubercle bacteria were performed in 91 of the patients All these examinations were negative and none of the 146 patients demonstrated clinical signs of tuberculosis Mantoux reactions with 1 TU (=tuberculin unit) and 10 TU (PPD State Serum Institute Copenhagen) were tested in 129 of the patients (Table VIII)

RESULTS

Radiographic intrathoracic manifestations

Of the 146 patients 129 (88%) had hilar adenopathy—bilaterally symmetrical as a rule presenting with polycyclic contours in all patients except four in whom it was mainly unilateral Ninety seven patients (66%) had isolated BHL 17 (12%) had isolated pulmonary lesions and 32 (22%) had hilar adenopathy+pulmonary lesions Only one patient with isolated pulmonary lesions was in the age group 31–50 years the other 16 patients were below

30 years The pulmonary lesions consisted of isolated infiltrates in one or both lungs or of wide spread mottled shadowing Of the 36 patients who had a follow up X ray in our department 20 showed regression 14 were unaltered and 2 showed pro gression the latter 2 patients belonged to the group BHL+pulmonary involvement One of them was treated with prednisone for a short period

Scalene fat pad biopsy

It appears from Table I that tissue suitable for histological examination was obtained in 99 of the 140 patients who had a scalene fat pad biopsy per formed In the 99 biopsies with suitable tissue typical epithelioid cell granulomas were found in 51 cases (52%) We analysed our material in relation to the way in which the biopsies were performed be cause there were some differences in the surgical technique in the first and second part of the 10-year period as described in Methods

Tissue from lymph nodes was obtained in 59 of 63 patients in the STS group and in 38 of 75 cases only in the GS group ($p<0.001$ χ^2 test) It is shown in Table II that epithelioid cell granulomas were demonstrated in 37 of the 59 patients in the STS group while in the GS group they were found in only 12 of 38 cases Thus it seems clear that lymph node tissue is obtained more frequently when the scalene fat pad biopsy is done in general anesthesia by a surgeon trained in this technique than when done in local anaesthesia by a less experienced surgeon Furthermore according to our results a lymph node tissue obtained by biopsy in the STS group contains epithelioid cell granulomas more of ten than a tissue obtained by biopsy in the GS group ($p<0.01$ χ^2 test)

Table II *Results of histological examination of lymph node tissue obtained by scalene fat pad biopsy in 99 patients*

D=detected ND=not detected

Biopsy group	No of biopsies	Granulomas D	Granulomas ND
STS	59	37	22
GS	38	12	26
Unknown	2	1	1
	99	50	49

Significance of the difference between STS and GS groups $p<0.01$

Table III *Scalene fat pad biopsy with suitable tissue obtained in relation to radiographic intra thoracic manifestations in 99 patients*

D=detected ND=not detected

	No of pats	Granulomas D	Granulomas ND
BHL without pulmonary involvement	64	25	39
BHL with pulmonary involvement	23	17	6
Pulmonary involvement without BHL	12	8	4

Table III correlates the presence of granulomas with the radiographic intrathoracic manifestations It will be seen that among 64 patients with isolated BHL granulomas were found in about 40% while in the other two groups the percentages were about 75 and 50 respectively of the scalene fat pad biopsies We have correlated these results with the surgical technique as shown in Table IV In the STS group granulomas were found in 21 of 37 patients with isolated BHL (scarcely 60%) This figure cor responds to the finding that in the total STS group granulomas were present in 37 of 59 patients (63%) In the GS group granulomas were found in only 4 of 26 patients with isolated BHL The skew dis tribution with the fewest patients with granulomas in the group with isolated BHL seems to be equalized by dividing the patient material accord ing to the surgical technique More patients with isolated BHL were found to have granulomas in the STS group than in the GS group there is still a tendency for more patients in the group with BHL+pulmonary lesions to have granulomas than in the groups with isolated BHL or isolated pul monary involvement

Liver biopsy

Table I shows that liver tissue was obtained by liver biopsy in 70 of 71 patients In 30 cases (43%) the biopsy specimen contained typical granulomas

In Table V the findings of granulomas obtained by liver biopsy are correlated to the radiographic intrathoracic manifestations in the same way as in Table III for the scalene fat pad biopsy It is seen that the occurrence of granulomas in liver biopsies among the three groups of patients (divided accord ing to the radiographic intrathoracic manifestations) is rather similar the figures being 20 of 45 in the

Table IV *Scalene fat pad biopsy in relation to surgical procedure and radiographic intrathoracic manifestations in 97 patients*

D=detected ND=not dete^cted

	STS group			GS group		
		Granulomas			Granulomas	
	No of pats	D	ND	No of pats	D	ND
BHL without pulmonary involvement	37	21	16	26	4	22
BHL with pulmonary involvement	14	12	2	9	5	4
Pulmonary involvement without BHL	8	4	4	3	3	0

group with isolated BHL 7 of 15 in the group with BHL+pulmonary lesions and 3 of 10 in the group with isolated pulmonary lesions

Other biopsies

Table I shows that suitable tissue was obtained in 13 patients by other biopsies Typical granulomas were found in 5 of these 13 biopsies Thus granulomas were found in 86 specimens altogether obtained by the above mentioned biopsies The 86 tissue specimens containing granulomas originated from 64 of the 146 patients each of them having at least one biopsy done as described

Comparison of biopsy results

Table VI compares the results of the scalene fat pad biopsy and the liver biopsy the two biopsies most frequently applied in this material The Table in—cludes the 59 patients in whom tissue suitable for ogical examination was obtained by both Granulomas were found more often in obtained by scalene fat pad biopsy than by liver biopsy but the difference was not statistically significant (χ^2 test) It will be seen that only 17

Table V *Liver biopsy in relation to radiographic intrathoracic manifestations in 70 patients*

D=detected ND=not detected

	No of pats	Granulomas	
		D	ND
BHL without pulmonary involvement	45	20	25
BHL with pulmonary involvement	15	7	8
Pulmonary involvement without BHL	10	3	7

patients had granulomas demonstrated by both biopsies and 14 patients had no granulomas demonstrated by either of the two biopsies

Biopsy complications

Among the 140 patients subjected to the scalene fat pad biopsy, one patient had transitory muscle pains localized to the biopsy site Another patient had a transitory partial paresis of the hand corresponding to that side of the neck on which the biopsy was done Two other patients developed slight brief infections in the wound after the biopsy In all these 4 cases the biopsy was performed in local anesthesia Among the 71 patients who had a liver biopsy done one patient developed a transitory fall in the BP in connection with the biopsy procedure and a few days later his temperature was slightly elevated No other complications were observed in relation to the biopsies

Other examinations

In the 71 patients in whom liver biopsy was performed the liver function was examined by various blood tests as shown in Table VII None of these patients had clinical signs of affected liver function or enlargement of the liver In the cases with pathological findings in liver function tests only minor deviations from the normal were found All 10 patients with slightly elevated basic phosphatases were below 25 years of age and these values therefore could not be regarded as pathological As shown in Table VII pathological values in liver function tests were found in the same frequency in the groups with and without granulomas in the liver biopsy The γ globulin concentration in plasma was measured in 71 of the patients and was found to be elevated in 18 10 of them had granulomas in the liver biopsy

ESR examined in 141 patients was elevated in 18 Serum calcium concentration examined in 88 patients was elevated in 3 In one case the level was 14 0 mg/100 ml this patient also had elevated serum creatinine concentration of 1 8 mg/100 ml and granulomas were demonstrated in his muscle biopsy as well as scalene fat pad biopsy He was treated with prednisone and in relation to this serum calcium and serum creatinine both normalized The other 2 patients had only slightly elevated serum calcium values (11 0 and 11 3 mg/100 ml) and were not considered to need treatment In one of these patients no lymph node tissue was obtained by the scalene fat pad biopsy but the histological examination revealed that the biopsy specimen consisted of normal parathyreoid tissue Serum creatinine was elevated in 3 of 83 patients One of these patients has been mentioned above and the other two had only slightly elevated serum creatinine (1 4 mg/100 ml) and no therapy was instituted

In one patient petechiae were found on admission He had a severe thrombocytopenia with a thrombocyte count of 2 520/μl which returned spontaneously to normal values within a few days This patient also had a positive toxoplasmosis neutralization reaction with a titer of 1 250 and granulomas were detected in his liver biopsy Another patient also had a positive toxoplasmosis neutralization reaction (titer 1 250 later decreasing to 1 50) The complement fixation reaction was vaguely positive 1 2 He had BHL but no granulomas were found in the scalene fat pad biopsy No other biopsies were performed It is not possible on the basis of these results to decide whether this patient had toxoplasmosis or sarcoidosis

Table VIII demonstrates that 59% of the 129 patients tested for tuberculosis had a positive tuberculin reaction with 1 and 10 TU independent

Table VI *Suitable tissue obtained by scalene fat pad biopsy and by liver biopsy in 59 patients*

	Liver biopsy		
Scalene fat pad biopsy	Granulomas detected	Granulomas not detected	No of pats
Granulomas detected	17	20	37
Granulomas not detected	8	14	22
No of pats	25	34	59

Table VII *Laboratory tests in relation to the results of liver biopsy in 71 patients*

D=detected ND=not detected

	Granulomas	
	D	ND
Decreased serum prothrombin	7	7
Increased serum alkaline phosphatase	5	5
Increased serum alanine aminotransferase	1	2
Decreased serum albumin	1	1
Decreased serum α 1-globulin	1	2
Increased serum α 1 globulin	0	1
Increased serum α 2-globulin	3	2
Increased serum β globulin	0	1
Increased serum γ globulin	7	5

of the presence of granulomas The difference is not statistically significant (χ^2 test)

Among the 73 patients who underwent a routine ophthalmologic examination 3 presented with pathological findings One had signs of previous uveitis one had chronic iridocyclitis in both eyes and one had iridocyclitis and typical granulomas of the iris in one eye Three weeks before the examination this patient had had slight ciliary pains and shunning of light The other 2 had had no eye symptoms

DISCUSSION

Chest X ray findings

Our chest X ray findings do not correspond entirely to those of other investigators (10 26 30 31) all of whom found a lower percentage of isolated bilateral hilar adenopathy and a slightly higher percentage of hilar adenopathy + pulmonary lesions than we did though the percentages of patients with isolated lesions are similar to the figures in our material The discrepancies are probably due to the fact that most of our patients are young and examined at the onset of the disease At that stage BHL is the most common manifestation although some cases of pulmonary sarcoidosis may occur without observed preceding BHL (27) On the other hand the patients in our material with isolated pulmonary lesions could have passed through the BHL stage unnoticed since it is well known and also confirmed in our material that this stage and the further course of the disease can be completely asymptomatic (27 28)

Table VIII *Tuberculin reaction in 129 patients*

D=detected ND=not detected TU=tuberculin unit

Tuberculin reaction	No of Pats	Granulomas	
		D	ND
Positive with 1 TU	29	13 } 34	16 } 42
Positive with 10 TU	47	21	26
Negative with 1 or 10 TU	53	19	34
p		n s	

As mentioned 12 of our patients had been diagnosed as BHL before the present admission We examined how these 12 patients dispersed among the 146 patients 8 of them had isolated BHL 2 had pulmonary lesions only and 2 had both In 5 of these 12 patients epithelioid cell granulomas were demonstrated by biopsy but this was not the case in the other 7 Thus the 12 patients do not differ significantly (p=n s χ^2 test) from the total material either in relation to radiographic intra thoracic manifestations or to the presence of granu lomas About 5 years before the present admission the two patients who now had isolated pulmonary lesions had BHL only The two with both BHL and pulmonary lesions a few years earlier had isolated BHL The remaining 8 patients with isolated BHL also had this manifestation a few months to a few years before the present admission The course of the disease in this unpretentious material of 12 pa ts seems to confirm that the disease starts with and tends to evolve through a stage of L+pulmonary lesions to the stage in which only pulmonary lesions can be demonstrated (27 30)

Scalene fat pad biopsy

Our percentage of granulomas detected by scalene fat pad biopsy is low compared to what others have found (26 27) But this can to some extent be ex plained by the difference in the surgical technique applied in the first and the second part of the 10 year period as discussed already Confining our selves to the biopsies in the STS group we find granulomas in 62% which is not far from the mean of 70% in other materials (24) This confirms that the scalene fat pad biopsy performed in a techni cally adequate way is a comparatively valuable method for supporting the diagnosis in patients with radiographic intrathoracic manifestations of sar coidosis

Liver biopsy

In 1943 liver biopsy was used for the first time as an aid in diagnosing sarcoidosis (1) Granulomas were found in the liver tissue in 2 of 4 patients with enlarged liver In later studies (2 12 13 23) it has been demonstrated that granulomas frequently are present in the liver of patients with radiographic intrathoracic manifestations of sarcoidosis even when there are no signs of affection of the liver function In these studies granulomas were found by liver biopsy with frequencies of 60–80% We found granulomas in the liver tissue in scarcely half the patients in whom liver biopsy was performed This is a lower percentage than in the studies above but as mentioned before almost all our pa tients were young apparently healthy persons The majority had isolated BHL and very few had palpa ble peripheral lymph nodes The liver function tests showed only small and few deviations from the normal There was no difference in the number of abnormal liver function tests in the patients with and without granulomas in the liver biopsy The rather high frequency of granulomas in the liver among our patients supports the concept that sar coidosis even in early stages is a systemic disease but is seldom accompanied by clinical symptoms from organs involved

Other biopsies

Four of the 13 other biopsies (Table I) were from the tonsils No granulomas were found in these 4 biopsies whereas 5 of the remaining 9 contained granulomas The results suggest that more biopsies (possibly repeated biopsies from the same organ) will make it possible to find granulomas in almost all patients with clinically suspected sarcoidosis

Comparison between scalene fat pad biopsy and liver biopsy

A comparison of the results of scalene fat pad biopsy and liver biopsy in the group of patients in whom both biopsies were done shows that granu lomas were found in about 60% of the scalene fat pad biopsies but in only 40% of the liver biopsies This difference may to some extent be explained by the fact that our patients were selected on the basis of radiographic intrathoracic manifestations of the disease To our knowledge only one other study has been reported with the primary purpose of compar ing the results between scalene fat pad biopsy and liver biopsy in a substantial number of patients with

clinically suspected sarcoidosis In that study Foti and Moser (7) performed both types of biopsies in 14 of their 58 patients with hitherto undiagnosed sarcoidosis Granulomas were found in 10 patients by liver biopsy and in 10 by scalene fat pad biopsy in 7 patients granulomas were demonstrated by both biopsies and in 3 by only one of them It cannot be finally concluded either on the basis of their or our study which of the two biopsy procedures is preferable for obtaining suitable tissue for histological examinations in patients without easily accessible clinical manifestations of sarcoidosis for instance palpable lymph nodes or eruptions of the skin An important factor to consider when choosing the biopsy procedure is the frequency of complications of the biopsy in question In our study neither the scalene fat pad biopsy nor the liver biopsy caused frequent or severe complications but in other studies both biopsy procedures have been reported to give serious complications even deaths

In younger and rather unaffected patients resembling those of our study the complications of both biopsy procedures can be expected to be few and insignificant (9 13 32)

Choice of biopsy procedure

The liver biopsy a m Menghini (25) is easy to perform and in our study almost always yielded suitable tissue The liver function tests are poor guidelines for selecting a biopsy procedure Scalene fat pad biopsy demands—as is clear from our study—a surgeon trained in this procedure but even then suitable tissue is obtained less frequently than by the liver biopsy As mentioned above the scalene fat pad biopsy must be considered of some value in diagnosing sarcoidosis especially when intrathoracic manifestations are present However in recent years the scalene fat pad biopsy has been applied less frequently in favour of biopsy through mediastinoscopy (3 4 17) This method has the advantage that sufficient lymph node tissue is obtained almost every time The mediastinal lymph nodes exclusively drain the intrathoracic organs while the supraclavicular lymph nodes also drain some extrathoracic regions e g part of the neck and the arm These circumstances probably contribute to the fact that granulomas are found more frequently in lymph node tissue obtained by mediastinoscopy than in such tissue obtained by scalene fat pad biopsy (22 26) Mediastinoscopy like scalene fat pad biopsy needs an experienced surgeon (17) It has the drawback of being liable to induce a more or less pronounced mediastinal fibrosis This fibrosis can make it impossible to repeat the examination in the same patient and increases the risk of complications with another mediastinoscopy (17) In contrast the scalene fat pad biopsy can be performed again in the same patient possibly on the opposite side of the neck

Other symptoms and signs

The occurrence of hypercalcemia in patients with sarcoidosis varies widely according to the literature (11 18 27 29) In some investigations the frequency was found to be 1–2% in keeping with our results but other authors report essentially higher values (about 15%) especially in patients with renal calculi and more or less impaired kidney function (19) Actually one of the reasons for the few cases of hypercalcemia and elevated serum creatinine values among our patients could be that most of them were young mainly with monosymptomatic BHL

As mentioned we had only one patient with severe thrombocytopenia However in a review (24) it is stated to occur in 1–2% of patients with sarcoidosis and another review (6) reports 5 deaths because of hemorrhages among 19 patients with thrombocytopenia

The decreased sensitivity to tuberculin is stressed as a characteristic feature in patients with sarcoidosis In some studies the intracutaneous tuberculin test was negative in two thirds of the cases (12 14 27) but such a high frequency of tuberculin negative cases has not been found in Northern Europe (8 21 29) In these reports 53–79% of the patients were found to be tuberculin positive in accordance with the 59% tuberculin-positive patients among those tested in our material On the basis of these results the tuberculin test seems of little value in diagnosing sarcoidosis

We found involvement of the eye in about 4% of our patients Higher percentages of eye lesions in sarcoidosis have been reported namely 14–33% of the patients examined (12 15 27 29) In most cases the ocular lesions comprise uni or bilateral uveitis and enlargement of the lacrymal gland but the sarcoid lesions may be localized to conjunctiva and sclera as well although these locations are less common The finding of granulomas in the iris as the only manifestation of sarcoidosis i

ported The patients with eye manifestations in other studies were on an average older than our patients

FINAL COMMENTS

The application of lymph node biopsy through mediastinoscopy has confirmed the concept that the radiographic finding of BHL nearly always is tantamount to the presence of epithelioid cell granulomas in the hilar lymph nodes The course of the disease from the BHL stage to the later stages is clinically and radiologically well described but the occurrence of granulomas in various intra and extrathoracic tissues at the different stages of radiographic intrathoracic manifestations is not known to any great extent Further studies with comparison of different biopsies in the same patients could shed more light on these problems

In this study the diagnosis of sarcoidosis is based primarily on the result of the chest X-ray and in about half of the cases supported by the presence of epithelioid cell granulomas in a biopsy specimen But as emphasized by Scadding (27) a greater diagnostic certainty is obtained if granulomas can be demonstrated in more specimens from different tissues and if the course of the disease in the individual patient can be followed over a longer period However for practical reasons it is difficult to fulfil these diagnostic criteria

A reliable way of diagnosing sarcoidosis will [illegible]bably have to wait until its etiology has been [illegible]ted a problem which is of course closely [illegible]ated to the fact that it has still not been possible to reach a generally accepted definition of the disease (16)

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Pattern of Enzyme Activity Following Acute Myocardial Infarction with Special Reference to γ-Glutamyl Transpeptidase

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ABSTRACT The present study on 55 consecutive patients with acute myocardial infarction (AMI) draws attention to the relationship between different enzyme maxima in AMI, with special reference to serum γ glutamyl transpeptidase (S-GT) In more than 60% of the patients the S-GT was increased during the hospital stay The S-GT rise nearly always began during the first days reached a maximum within 5-8 days and normalized within 2-3 weeks We failed to find the late increase in S-GT reported by others The rise of S-GT is particularly common in patients with inferior infarction with or without right ventricular involvement We conclude that S-GT activity is not a useful early or late indicator of AMI but a very sensitive test for hepatic dysfunction in patients with AMI

The determination of serum enzymes has become an indispensable tool in the coronary care unit (CCU) Since 1954 when La Due Wroblewski and Karmen first measured the activity of S-ASAT (serum aspartate aminotransferase) in acute myocardial infarction (AMI) this and other enzymes have been widely used as diagnostic aids

The increase of S-ASAT to its maximum within one or two days after onset of symptoms accompanied by a rise of lactate dehydrogenase the heatstable fraction (LD/LD_1) and serum creatine phosphokinase (S-CK) but with a little change in S-ALAT (serum alanine aminotransferase) is well known However the relation between these enzyme maxima may differ depending on the release of enzymes from other organs mainly from the liver In some cases this will make the diagnosis of AMI difficult or even impossible Furthermore assessment of infarct size by means of the peak enzyme level will be difficult

Some enzymes e g S-CK and the heatstable isoenzymes of LD have been shown to be somewhat more specific than the aminotransferases for the diagnosis of AMI Not even these serum enzymes are however specifically found in the heart and several authors recommended a modified cardiac enzyme panel for investigation of chest pain (2 6 10 13 14 18 23) This will permit greater accuracy in the interpretation of enzyme changes and increase the possibility of deciding when other organs have contributed to the enzyme rises

This study which is part of a program of research on enzymatic activity after AMI was performed to analyze the relationship between different enzyme maxima in AMI with special reference to the influence of γ-glutamyl transpeptidase (S-GT) and serum alkaline phosphatase (S-ALP) from the liver during the acute stage of AMI

MATERIAL AND METHODS

The patient population consisted of 55 consecutive patients with AMI 40 men and 15 women The criteria for admission and diagnosis adopted at our CCU have been presented elsewhere (23) S-ASAT S-ALAT LDH S-CK S-ALP and S-GT were analyzed routinely on admission and every 12 hours while the patients were in the CCU and twice a week for the remaining hospital stay Analyses were made with a Reaction Rate Analyzer (LKB 8600) connected to an evaluation unit (Optilab Bo Philip Instrumentation Stockholm) Reference values for enzymes used are summarized in Table I

RESULTS

Relation between the enzyme maxima

The relation between the peak values of S–ASAT and S–ALAT is shown in Fig 1 The correlation is poor with a wide variation in the S–ALAT values (r=0 43)

In some patients with high peak values of S–ALAT it might reasonably be suspected that the liver contributed to these To study whether this could be the case the patients were divided into two groups one with a rise of S–GT suggesting hepatic engagement the other with normal S–GT during hospital stay The S–GT was increased in 34 patients (63%) and remained normal in 21 The mean level of the maximal S–ALAT values was 47 U/l in patients with S–GT elevation compared with 35 U/l in those without, while S–ASAT maximum was 174 and 164 U/l respectively These differ ences were not significant There was no correla tion between the maximal S–ASAT and S–GT val ues (r=0 06) (Fig 2) At low S–ASAT maxima the S–GT may be elevated and at very high S–ASAT maxima it may be normal (Fig 2) A weak relation ship between S–ALAT and S–GT (r=0 20) can be observed It is possible that the higher S–ALAT values depend on leakage from the liver (Fig 3) If so S–ALAT values with simultaneous S–GT eleva tion may be partly influenced by enzyme leakage m the liver The relation between S–ASAT max and S–CK maxima in patients with normal T is shown in Fig 4 The correlation was highly ignificant (r=0 93) However if S–GT was ele vated the correlation was less good (Fig 5) sup porting the possibility that the S–ASAT value had been influenced by leakage from the liver

Elevation was less common in S–ALP than in S–GT (Fig 6) and all patients with increased S–ALP had a rise of S–GT but not vice versa A typical course of the enzymatic pattern in a patient with a rise of S–GT is shown in Fig 7 The S–GT increases within 2–3 days the maximum is reached on the 5th–8th day and normalizes within 2–3 weeks after the acute attack Fig 8 shows that even in patients with rather large infarctions the S–GT values can be within the normal range throughout the hospital stay

Table I *Normal values for the enzymes*

	Normal range	Borderline
S–ASAT	10– 35	35– 40
S–ALAT	10– 35	35– 40
LDH	100–350	350–400
LDH_1	50–250	250–300
S–CK	10– 50	50– 80
S–ALP	10– 30	30– 35
S–GT	10– 25	25– 30

Table II *Relation between rises in S–GT and the infarction site according to ECG*

		S–GT (U/l)			
		<30		>30	
Infarction site	N	n	%	n	%
Anterior anterolateral lateral	29	15	52	14	48*
Inferior inferolateral antero inferior	18	1	6	17	94*
Uncertain	8	5	53	3	47

* $p<0\ 01$

Relation between rises of S–GT and the infarction site according to ECG

Anterior AMI was found in 29 patients inferior in 18 and inconclusive in 8 Four of the patients with inferior AMI had ST–T elevation in lead CR_4R thought to reflect extension of the infarction into the right ventricle The S–GT was increased in 14 of the 29 patients (48%) with anterior wall infarction compared with 17 of the 18 (94%) with involvement of the inferior wall (p<0 01) (Table II)

DISCUSSION

Koch (15) pointed out the necessity of discussing the quotients of different enzymes in patients in whom the enzyme picture is not conclusive Since the maximal value of S–ASAT has been found in several reports (4 5 8 12 21) to be connected with the prognosis it is important to elucidate whether this maximum solely depends on the size of the infarction or whether it also reflects enzyme leak age from other sources

In more than 60% of the present AMI patients the S–GT was increased during the hospital stay This finding is in agreement with several previous studies (3 11 17 19 20 22) Coodley (6) however found only 6 patients with rises of S–GT activity among 38 with proven myocardial infarction The S–GT rise in our study nearly always began during the first days reached its maximum within 5–8 days

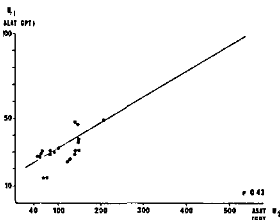


Fig 1 Relation between the peak values of S-ASAT and S-ALAT

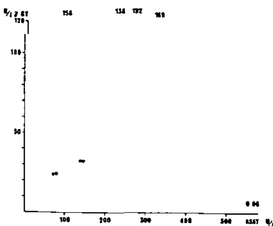


Fig 2 Relation between maximal S-ASAT and S-GT

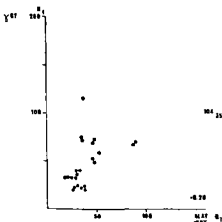


Fig 3 Relation between maximal S-ALAT and S-GT

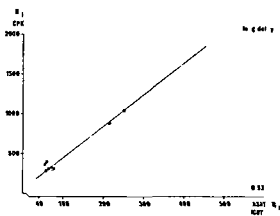


Fig 4 Relation between the peak values of S-ASAT and S-CK in patients with normal S-GT values

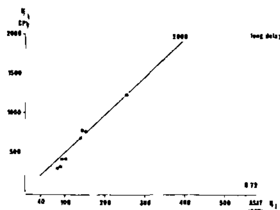


Fig 5 Relation between the peak values of S-ASAT and S-CK in patients with elevated S-GT

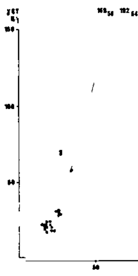


Fig 6 Relation between maximal S-ALP and S-GT

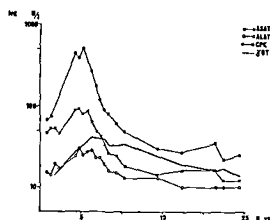


Fig 7 The enzymatic pattern in a patient with a rise of S-GT

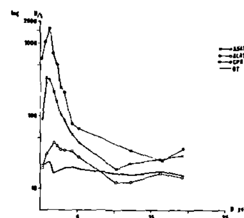


Fig 8 The enzymatic pattern in a patient with normal S-GT values throughout the hospital stay

was normalized within 2–3 weeks in contrast to a later rise described by others (11 17 19, 22) Those who have reported a high incidence in AMI have suggested that S-GT originates from the heart with the assumption that its increase might be related to the repair process This theory is supported by the demonstration that walls of new capillaries contain high levels of S-GT (7) Furthermore Ravens et al (17) found S-GT also in the lysosomes of invading leucocytes in dogs with experimental infarction However we like some others (3 6) failed to find a late increase in S-GT and we also failed to find it in all patients with AMI irrespective of infarct size suggesting that this finding is not related to reparative processes in the myocardium

In the present study, patients with increases in S-GT also had an S-ALAT maximum which was slightly higher compared with the S-ASAT maximum during the acute stage of AMI In uncomplicated AMI rises in S-ALAT roughly follow the rises in S-ASAT but do not exceed the upper normal level unless the infarction is extensive We have previously reported repeated observations of a late rise in S-ALAT, about a week after the onset of symptoms and exceeding simultaneous S-ASAT values These rises of S-ALAT were associated with elevated S-ALP levels and slightly impaired BSP loading improved 5–9 months after the AMI (9)

The present study showed a very good correlation between S-CK maximum and S-ASAT maximum in patients without a simultaneous increase of S-GT supporting the concept that in patients without S-GT elevations the S-ASAT values represent a more distinct index of the magnitude of the infarction Furthermore there is a good correlation between the infarct size at autopsy and S-ASAT, LD and LD_1 in patients without elevated S-ALAT which is not the case when S-ALAT is elevated (8)

Schmidt and Schmidt (20) considered that more than 95% of even small disturbances of the liver can be revealed by S-GT elevations and they also stated that S-GT is more sensitive than S-ALP in hepatic impairment This agrees well with our findings that all patients with increased S-ALP also had a rise of S-GT but not the reverse

Abnormalities in other liver function tests in AMI have been reported earlier (1 9 16) It seems reasonable to assume that in AMI enough impairment of hepatic function might occur to produce a rise in S-GT even without clinical heart failure Extensive myocardial damage and the location of the necrosis particularly infarction of papillary muscles and right ventricular infarction may be of hemodynamic significance This is borne out by the fact that nearly all patients with involvement of the inferior wall of the left ventricle with or without right ventricular involvement had S-GT elevations but only half of those with predominantly anterior infarction of the left ventricle It is noteworthy that 5 of 6 patients with a rise of S-GT in Coodley s report (6) also had inferior infarctions

We conclude that in contrast to some previous reports S-GT activity is not a useful late indicator of AMI but rather a very sensitive test for hepatic dysfunction in patients with AMI even without associated clinical signs of hepatic or heart failure The rise of S-GT is particularly common in patients with inferior infarction with or without right ventricular involvement, suggesting that one factor re

lated to hepatic impairment might be right sided heart failure S-GT elevation is not uncommon and we recommend some sort of liver test in every case with AMI S-ALP S-GT or S-ALAT the latter in comparison with the S-ASAT values

ACKNOWLEDGEMENT

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Announcements

The XXIV Annual Colloquium on Protides of the Biological Fluids will be held in Brugge, Belgium April 27–May 1 1976 Following topics will be covered Pregnancy associated proteins Carcino-fetal and carcino-placental proteins Detection and quantitation of proteins by molecular amplification

Further information Colloquium Protides of the Biological Fluids Simon Stevin Instituut Jerusalemstraat 34 B 8000 Brugge Belgium

Tenth Miles International Symposium—impact of recombinant molecules on science and society—will be held at the Kresge Auditorium Massachusetts Institute of Technology Massachusetts USA June 8–10 1976

Further information E G Bassett Ph D Miles Laboratories Inc Elkhart Indiana 46514 USA

First International Symposium on HLA and Disease (Predisposition to disease and clinical implications) will be held at the Palais des Congrès, Paris France 23–25 June 1976

Chairmen J Dausset and A Svejgaard

Secretaries L Degos and J Hors

Further information Congres Services, 1 Rue Jules Lefebvre F 75009 Paris France

The X International Congress of Gastroenterology and the III European Congress of Gastrointestinal Endoscopy will be held in Budapest Hungary, June 23–29 and June 30–July 2 1976 respectively

Secretary general Prof I Wittmann

Secretary Doz G Prónay

Further information Motesz Congress Bureau H 1361 Budapest P O B 32 Hungary

Acta med scand Vol 199 pp 223-228 1976

Vectorcardiographic–Hemodynamic Correlations in Adult Aortic Stenosis

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ABSTRACT Thirty nine vectorcardiographic (VCG) data from 45 patients with pure adult aortic stenosis have been tested as to their ability to reflect quantitatively the peak systolic left ventricular pressure (LVPSP) the left ventricular end diastolic pressure (LVEDP) and the X ray estimated heart volume VCG was recorded with the axial lead system and simple and multiple linear regression analyses were applied Eight VCG data correlated significantly ($p<0\ 001$) with LVPSP, the best indicator being the maximum posterior dislocation in the Z lead ($r=0\ 65$) Through multiple regression analysis a formula was derived which gave a correlation coefficient between observed and calculated pressures of 0 82 The best indicator of LVEDP was the maximum positive P amplitude in the X lead ($r=0\ 41$) The relationship was, however, too poor to have practical significance A good correlation was found between ST segment dislocation and heart volume ($r=0\ 65$), in good accordance with previous observations as to the effect of right ventricular dilatation on the ECG The study illustrates how ventricular volume and pressure exert different effects on the ECG, and how all the important hemodynamic aspects in aortic stenosis to some degree are reflected Only the pressure correlations have, however, practical importance

Several studies indicate that the conventional 12 lead ECG has a limited ability to assess the degree of left ventricular hypertrophy (LVH) in aortic stenosis (5 12 31) A number of investigators therefore turned to vectorcardiography (VCG) hoping that an improved recording of dipolar activity in the heart might improve the diagnostic performance (6 13 17 18 26 30) In general the results of this approach have been promising with regard to congenital aortic stenosis but in acquired stenosis VCG has not been documented to be of major value

We have recently reported an improved prediction of right ventricular systolic pressure in patients with congenital lesions which impose an overload on the right ventricle by the use of combined VCG data (28 29) The present report describes a similar approach in a group of patients with adult aortic stenosis

The aims of the study were 1) To search for VCG data which could optimally predict hemodynamic data Some of the data chosen had previously not been tested in this respect 2) To test the ability of data combinations to improve these results 3) To study the comparative effects of left ventricular pressure and volume loads on the ECG

MATERIAL AND METHODS

Patients

Forty five patients with pure aortic stenosis were studied No selection was made as to the postulated etiology of the lesion Three patients below 30 years probably had congenital aortic stenosis In most of the others no definite etiology could be established (34) The mean age of the patients was 55 years

Hemodynamic data

All the patients had been subjected to left heart catheterization including a technically satisfactory left ventricular pressure tracing and cineangiograms both from the aortic root and the left ventricle Selective coronary arteriography was performed on all patients with possible angina or other clinical evidence of coronary heart disease

The following requirements were set for admission to the study 1) No clinical hemodynamic or angiographic evidence of mitral valve disease or subaortic stenosis should be present 2) A diastolic murmur indicating aortic insufficiency should not be heard by experienced clinicians Angiogram from the aortic root should indicate none or only slight aortic regurgitation 3) Patients with more than 50% stenosis of a coronary artery were excluded 4) The QRS duration should not exceed 0 12 sec

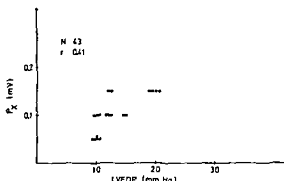


Fig 5 Relationship between LVEDP and the maximum positive P amplitude in lead X

(Fig 4) outside the 95% confidence interval of the best simple correlation The performance of the formula for differentiating between patients with LVPSP below and above 200 mmHg was 0 87

Other correlations

As expected almost identical VCG variables were found to correlate with the peak systolic valvular gradient as with the LVPSP but the correlations were in general poorer This is in accordance with the fact that the gradient exerts no primary influence upon the myocardium

As expected the correlations between VCG data and LVEDP were much poorer than with LVPSP The best individual correlation was found with the mum positive P amplitude in lead X (Fig 5) ly a reflexion of the left atrial dilatation oc during elevation of the ventricular end diastolic pressure It is noteworthy that this VCG datum did not correlate at all with LVPSP ($r=0\ 00$) All other VCG data which correlated with LVEDP had better correlations with LVPSP

As seen from Table I still other VCG data correlated with the heart volume the best being various expressions of the ST–T segment dislocation (Fig 6) The correlation between secondary rightward deflections in lead X (Table I) probably reflects only the same phenomenon The X ray volume did also correlate to some extent with LVPSP and LVEDP while there was no such correlation with the P wave amplitude It is also noteworthy that an almost significant correlation between QRS duration and heart volume was found in spite of the absence of correlation between this parameter and the pressures

DISCUSSION

LVPSP correlations

This study has implications both for practical diagnosis of adult aortic stenosis and for theoretical electrocardiography The practical results are mainly confined to the VCG prediction of LVPSP The correlations using simple VCG data demonstrate a moderate although highly significant, ability to predict this pressure The results are superior to those achieved by conventional ECG in adult aortic stenosis (5 35) and in hypertension (14) and also to most studies comparing left ventricular mass or weight with conventional ECG data (32 33) The best simple correlations are close to those found by Vine et al (36) between angiographically determined left ventricular volume and mass data on the one hand and VCG on the other Pressure prediction was however not significant in their study as would be expected from the heterogeneous patient material Compared with the work of Ellison and Restieaux (10) the present results are superior to those obtained by them with Frank lead VCG but inferior to those obtained with a grid system In several of the studies mentioned the material was far less homogeneous as to the etiology of the LVH than in the present The results are similar to those obtained by Postell et al (26) in a much smaller material of patients with pure aortic stenosis using the Helm VCG system and by Hugenholtz et al (18) with the cube system The correlations are however not by far as good as in the classical studies of Gamboa et al (13) and Hugenholtz and Gamboa (17) who found correlation coefficients between LVPSP and simple VCG data

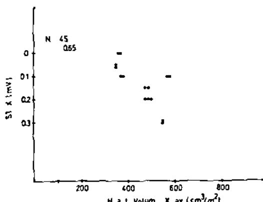


Fig 6 Relationship between heart volume estimated by conventional X ray and the ST segment depression in lead X

up to 0 88 in congenital aortic stenosis Holt et al (16) have reported excellent quantification of LVH by multiple dipole ECG The present finding of weaker correlations with the pressure gradient than with the LVPSP is in accordance with previous reports Although a precise comparison of the different works is not feasible the results of the present study indicate that VCG has a clear ability to predict LVH also in adult stenosis and that this ability probably is superior to that of conventional ECG

The results of the multiple regression analysis must be interpreted with care since the material is comparatively small in proportion to the number of VCG data applied (7 25) This is a general problem in all available studies originating in the difficulty to sample a sufficient amount of precisely diagnosed cases The results indicate however a significant improvement of pressure prediction with data combinations This conclusion needs confirmation with new patient samples

Previously three groups have applied this statistical approach to the ECG-VCG diagnosis of LVH Through the combination of three ECG-VCG data Postell et al (26) improved the VCG-LVPSP correlation from 0 70 with the best simple datum to 0 82 The small number of patients in their study ($n=22$) do however scarcely warrant the use of this method Vine et al (36) used all available data in the computation intending more to search for maximum informational content than for a practical result Their study indicated that VCG contained somewhat more information regarding left ventricular mass and volume than ECG but the differences were small Ellison et al (9) improved prediction of left ventricular weight through the combination of 6 grid lead VCG variables the correlation coefficient increasing from 0 85 to 0 95 They also used non linear regression analysis and the number of variables applied was large

Other correlations

The relationships disclosed between VCG data and heart volume (Fig 6) and LVEDP (Fig 5) are particularly important for the more theoretical question which hemodynamic factors in ventricular hypertrophy and dilatation influence the different ECG changes? The observation that the maximum leftward P amplitude correlated with the LVEDP confirms previous reports that P wave data may be a useful index of left atrial pressure and thus of the left ventricular functional state (11 15 19) It is of interest that the P wave amplitude had no relation to the magnitude of the pressure load It is therefore an expression of the response of the left ventricle to the load more than of the load itself It is possible that a closer analysis of P wave data might have improved the correlations

Similar considerations may be made regarding the observed stronger correlation between ST segment data and the heart volume than between these data and pressure This observation is in good agreement with our previous reporting of the ST segment dislocation as the VCG datum which correlates best with shunt size in atrial septal defects (28) This suggests that ventricular dilatation exerts its effect upon the ECG predominantly through a progressive dislocation of the ST segment When the right ventricle is involved the dislocation is mainly backwards when the left ventricle is dilated it is mainly to the right

It is also of interest that like in right ventricular overload (28) the QRS duration tended to correlate with heart volume but not with pressure This indicates that the prolongation of the QRS duration during LVH at least up to 0 12 sec may be caused primarily by progressive dilatation and not by structural changes of the conductive system Similar conclusions have been drawn regarding the right ventricle (4)

In conclusion both LVEDP and ventricular volume as such have been found to modify the one to one relationship between muscle mass and ECG response in LVH Thus all essential hemodynamic aspects in aortic stenosis are to some extent independently reflected in the ECG Since the association with LVEDP is poor and X ray data are directly available only the estimation of LVPSP from VCG data is of practical importance

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The Thyroid in Ulcerative Colitis and Crohn's Disease

V Triiodothyronine Effect of Corticosteroids and Influence of Severe Disease

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ABSTRACT **The concentrations of triiodothyronine (T_3), thyroxine (T_4) and thyroxine binding globulin (TBG) have been measured in serum of 20 patients with ulcerative colitis or Crohn s disease The patient group was compared with 20 healthy control subjects matched for sex and age The concentrations of T_3 and T_4 were similar in the two groups but TBG in serum was higher in the patient group, mainly due to the high TBG levels in the female patients The concentration of T_3 in serum was lower in the severely ill patients than in those who were mildly–moderately ill while T_4 and TBG were not affected by the severity of the disease The concentration of T_3 was lower in the corticosteroid treated patients than in those who did not have such treatment, just like the TBG level However, TBG was not subnormal in the corticosteroid treated patients whereas the serum concentration of T_3 was T_4 in serum was not affected by treatment with corticosteroids These findings indicate that the metabolisms of T_4 and T_3 are influenced differently by corticosteroids**

In endemic goitre areas where iodine deficiency is common the serum triiodothyronine (T_3) concentration has been reported to be raised (4 16) or normal (13) In patients with ulcerative colitis (UC) or Crohn s disease an increased prevalence of iodine deficiency has been reported (8) Hence it seemed worthwile to measure the serum concentration of T_3 in patients with UC or Crohn s disease In the same patients and control subjects as reported here the serum concentrations of thyroxine (T_4) and thyroxine binding globulin (TBG) were also measured on the same serum samples Those results have in part been reported earlier (10)

MATERIAL AND METHODS

The patient group consisted of ten women and ten men with UC or Crohn s disease The diagnoses were based on the clinical history the radiological findings the findings at sigmoidoscopy with rectal biopsy and in nine patients the findings at subsequent operation together with histological examination of the operation specimens Eight of the UC patients had extensive or universal disease as judged radiologically and three had distal colitis Of the patients with Crohn s disease four had extensive colonic disease three had widespread small bowel disease and two had ileo-caecal involvement

Ten of the patients four women and six men were being treated with oral or parenteral corticosteroids (30–60 mg prednisolone daily) while the remaining ten patients did not receive such treatment Ten of the patients (5 women 5 men) had lost considerable weight and were on clinical grounds judged to be severely ill Six of these patients were being treated with corticosteroids The remaining ten patients were considered to be mildly–moderately ill Four of them were receiving treatment with corticosteroids None of the patients had any symptoms of functional thyroid disease and none was receiving any drugs known to influence the thyroid function apart from the corticosteroids The mean age of the patient group was 32 2 years (range 18–66)

This group of patients was compared with 20 healthy control subjects (10 women 10 men) none of whom was taking the contraceptive pill nor receiving any other medication The mean age was 31 9 years (range 21–55)

The concentration of T_3 in serum was estimated according to the method of Gharib et al (5) modified as follows The incubation volume was 300 µl giving a shorter incubation time and swine immunoglobulin to rabbit IgG was used as precipitating antibody The concentration of T_4 in serum was determined using a method for competitive protein binding (15) slightly modified by the use of purified TBG as the binding protein The maximum thyroxine binding capacity of TBG was measured by agar gel electrophoresis at pH 8 6 with trismaleate as buffer (6)

To exclude the possibility that prednisolone in some

Table I T_3, T_4 and TBG in serum in the patients
m = mildly–moderately ill patients s = severely ill patients

Pat no	Severity of the disease	Treatment with corticosteroids	T_3 (1 8–3 0 nmol/l)	T_4 I (2 9–6 3 μg/100 ml)	TBG (15–25 μg T_4/100 ml)
Females					
1	m	–	2 3	4 7	26
2	m	–	2 7	6 2	37
3	m	–	2 9	6 7	40
4	m	+	2 1	5 2	26
5	m	+	1 0	2 9	25
6	s	–	2 4	4 6	23
7	s	–	2 8	5 6	39
8	s	–	1 5	4 7	25
9	s	+	0 5	2 8	24
10	s	+	2 1	3 9	22
Mean			2 0	4 7	28 7
S E			0 3	0 4	2 2
Males					
11	m	–	3 0	3 5	26
12	m	–	3 2	6 9	28
13	m	–	3 2	3 4	20
14	m	+	1 3	2 0	15
15	m	+	2 4	3 9	23
16	s	–	1 1	2 5	17
17	s	+	1 4	4 9	29
18	s	+	1 0	7 0	22
19	s	+	0 8	2 2	15
20	s	+	1 3	3 6	18
Mean			1 9	4 0	21 3
S E			0 3	0 6	1 6
t			1 07	0 40	2 68
p			N S	N S	<0 02

could interfere with the chemical analysis of T_3 in m the following experiments were performed The T_3 oncentration was estimated on a pooled serum sample before and after adding prednisolone sodium succinate in concentration increasing from 0 2 to 20 μg/ml In two patients not included in the material presented above the serum T_3 concentration was estimated before and 30 min *after the administration of 20 mg prednisolone sodium* succinate i v

RESULTS

The individual results for the patients are given in Table I T_3 and T_4 in serum were similar in male and female patients but TBG was higher in the females However, it is worth mentioning that nine of the 20 patients had subnormal serum concentrations of T_3

Table II shows that the total patient group had much the same concentrations of T_3 and T_4 in serum as the control group but TBG was higher in the patient group Patients who received treatment with corticosteroids had lower serum T_3 concentration than patients who did not have such treatment and also than the control subjects The serum T_4 concentration was not significantly affected by treatment with corticosteroids TBG in patients who were not receiving treatment with corticosteroids was higher than both in those who had such treatment and the control subjects

Table III shows that T_3 in serum was lower in the severely ill patients than in those who were judged to be mildly–moderately ill T_4 in serum and TBG were similar in these two patient groups The serum T_3 concentration was significantly lower in the severely ill patients than in the control subjects ($t = 2\ 68$ $p < 0\ 02$)

Tables IV and V show that prednisolone did not interfere with the chemical analysis of T_3

Table II T_3 T_4 and TBG in serum in patients with ulcerative colitis and Crohn s disease and in controls

S E M within parentheses

	T_3 (1 8–3 0 nmol/l)	T_4 I (2 9–6 3 μg/100 ml)	TBG (15–25 μg/100 ml)
I Patients not treated with corticosteroids (*n* = 10)	2 5 (0 2)	4 9 (0 5)	28 1 (2 5)
II Patients treated with corticosteroids (*n* = 10)	1 4 (0 2)	3 8 (0 5)	21 9 (1 5)
III All patients (*n* = 20)	2 0 (0 2)	4 4 (0 3)	25 0 (1 6)
IV Controls (*n* = 20)	2 1 (0 1)	4 2 (0 2)	19 3 (0 9)
Statistical significance of the differences			
I–II			
t	3 75	1 55	2 14
p	<0 01	N S	<0 05
III–IV			
t	0 79	0 52	3 15
p	N S	N S	<0 005
I–IV			
t	1 53	1 72	3 31
p	N S	N S	<0 005
II–IV			
t	3 20	0 73	1 54
p	<0 01	N S	N S

DISCUSSION

Earlier studies have shown that the PBI in serum was lower in endemic goitre areas than in areas without endemic goitre (1 14) The subjects studied in those two reports were extremely iodine depleted with much lower urinary iodine excretion than patients with UC or Crohn's disease (8) This is also illustrated by the fact that the frequency of thyroid enlargement in patients with UC (9) was much lower than that which is usual in endemic goitre areas Although the iodine state was not studied in the patients in the present report there is no reason to believe that it differed in these patients from those reported earlier (8) The less pronounced severity of iodine depletion in UC and Crohn's disease may be the reason why the serum T_4 was normal in the patients studied However it is possible that iodine deficiency is not the only cause of subnormal serum T_4 concentration in endemic goitre areas as the serum T_4 concentration in goitrous subjects in an endemic goitre area varied in different villages (13) This finding indicates that some further factor than iodine deficiency may be

Table III *T_3 T_4 and TBG in serum in severely and mildly–moderately ill patients*

S E M within parentheses

	T_3 (1 8–3 0 nmol/l)	T_4-I (2 9–6 3 µg/100 ml)	TBG (15–25 µg/100 ml)
Mildly–moderately ill patients (n=10)	2 4 (0 2)	4 5 (0 5)	26 6 (2 3)
Severely ill patients (n=10)	1 5 (0 2)	4 2 (0 5)	23 4 (2 2)
t	2 76	0 51	1 01
p	<0 02	N S	N S

Table IV *T_3 with increasing prednisolone concentration in serum in vitro*

Prednisolone concentration (µg/ml)	T_3 (nmol/l)
20	2 4
5	2 4
1	2 7
0 2	2 3
0	2 2

Table V *T_3's (nmol/l) before and 30 min after 20 mg prednisolone i v*

Before	30 min after
2 0	2 1
2 1	2 1

of importance for determining the thyroid hormonal pattern in serum Such a factor could perhaps be a goitrogenic factor in the local food

The question of the serum T_3 concentration in iodine deficiency does not seem to be definitely settled as both high (4 16) and normal values (13) have been reported In the present study the serum T_3 concentration was similar in the patient and the control groups It was also the same in male and female patients although the serum TBG level was higher in the females

Patients who were considered clinically to be severely ill had lower serum T_3 than both the mildly–moderately ill patients and the control subjects This finding confirms recent reports on low serum T_3 concentrations in patients with severe chronic disease (2) and severe liver cirrhosis (3) Some of our patients had a very low serum T_3 concentration but they were not clinically hypothyroid and they had normal TSH values This indicates that both T_4 and T_3 are metabolically effective Our observations do not support the hypothesis that T_4 is an inactive prehormone which exerts its effects only when it has been converted to T_3

Treatment with corticosteroids appeared to be perhaps even more important than the severity of the disease The serum T_3 concentration in corticosteroid treated patients was lower than in patients who did not have such treatment and also lower than in the control subjects The in vitro and in vivo experiments showed that this was not due to an interference of corticosteroids with the chemical analysis of T_3 Neither could it be due to a corticosteroid induced reduction of the serum TBG level which has been reported to decrease during corticosteroid treatment (12) as the serum TBG concentration was normal in the corticosteroid treated patients Neither could a corticosteroid induced expansion of the plasma volume be the cause because then the serum T_4 concentration should have been significantly lower too which was not the case These findings indicate that the metabolisms of T_4

and T_3 are influenced differently by corticosteroids To our knowledge no studies have appeared on the effect of corticosteroids on the serum T_3 concentration However one study indicated that corticosteroids exert a suppressing effect on the secretion of T_3 from the thyroid gland (11) It is possible that *such a suppression of the T_3 secretion from the* thyroid gland was the cause of the low serum T_3 concentration in the corticosteroid treated patients with UC or Crohn s disease Another possible explanation is that corticosteroids in some way interfere with the conversion of T_4 to T_3

Laboratory results of serum T_4 and the T_3 uptake *test (T_3-test) compatible with hyperthyroidism in* euthyroid patients with UC or Crohn s disease have been reported (7 10) This condition has been called pseudohyperthyroidism One of the patients with Crohn s disease reported earlier who had a high serum T_4 concentration and a high T_3-test result (10) was included in the present study and *his serum T_3 concentration was subnormal (1 0* nmol/l) This indicates that the serum T_3 concentration may be of value in doubtful situations to separate pseudohyperthyroidism from true hyperthyroidism

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Myxedematous Madness without Myxedema

Selective Defect of TSH Release on TRF Loading in a Young Woman with a History of Severe Depressive Illness Cured with Thyroid Hormone Replacement Therapy

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ABSTRACT A young woman, whose psychiatric history covered 16 years, has been treated several times as in patient for psychotic depressions which were finally cured with thyroid replacement therapy Recent reports of the connection between depression and disturbances in the hypothalamic pituitary thyroid axis are discussed The authors question the suggestion that selective pituitary insufficiency and a defect in TSH release on TRF loading are rare phenomena

Psychiatric symptoms in acquired hypothyroidism are well recognized A general retardation of cognitive and motoric functions is said to be characteristic but a panorama of psychotic manifestations may also be seen Besides illusional and hallucinatory experiences of all sensory modalities paranoid delusions can occur Occasionally hypothyreosis is found together with manic or catatonic episodes (2) Relevant in this context is the notion by Crammond (4) that all organic psychoses be they acute or chronic affect all the mental processes cognition mood and behaviour All three aspects of the brain function will be affected but the degree of involvement of each component will vary from person to person and also according to the duration and development of the illness or as Bleuler (2) puts it es gibt keine spezifischen psychopathologischen Krankheitsbilder für jede der vielen zugrundeliegenden Körperkrankheiten und körperlichen Noxen

Asher (1) described 14 cases of organic psychosis due to myxedema in 1949 At that time it was impossible to confirm the diagnosis chemically and the author had to rely chiefly on clinical findings No uniform type of psychosis was found but dominant findings were confusion with disorientation persecutory delusions and hallucinations Asher concludes that there is no specific myxedematous psychosis but paranoid delusions seem to be notably common Also Easson (5) denies that there are findings typical of myxedematous psychosis but he too stresses the recurring findings of paranoid thoughts

In recent years there have been some reports on the efficiency of supplementing the tricyclic antidepressive drug treatment of depressive illness with triiodothyronine (12 15) Parallel with the increasing insight into the neuroendocrinology of the hypothalamus and its releasing hormones of which the thyroid stimulating hormone (TSH) releasing factor (TRF) hitherto clinically has proved the most fruitful (7) there has also been some interest in a possible antidepressant action of TRF (13) These studies led to the suggestion of a defect in the hypothalamic pituitary system with regard to TRF and TSH in some cases of depressions (8)

This paper describes a patient without clinical myxedema but with a psychiatric history compatible with the descriptions of myxedematous psychosis and with findings indicating a selective lesion on the pituitary level

CASE REPORT

The patient a woman aged 27 years Negative family history of psychiatric illness and endocrinological disease No neurotic symptoms during early childhood At age 9 years treated for a short period in a paediatric clinic for

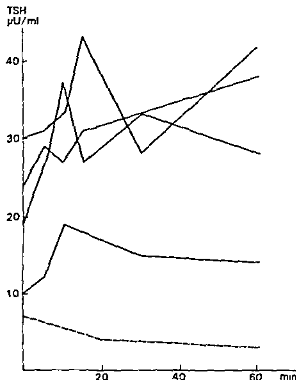


Fig 1 Different individual time courses of serum TSH levels in four normal subjects from the series of Karlberg et al (9) (—) and the present patient ( ) after i v administration of 0 1 mg TRF

rheumatic fever manifesting in arthritis and myocarditis but with no recurrences or sequelae During these years her parents divorced When she was aged about 10 years she began to complain of tiredness backache and pre cordial pain As no organic cause could be found she was to a children s psychiatric clinic where her symp- were interpreted as a depressive reaction in a neuro- child and her parents divorce was thought to be of relevance During the following ten years she was treated by a child psychiatrist either as in or out patient The dominant symptoms were extreme shyness mimic and motoric retardation and dysphoria She developed an im pressive secondary gain engaging not only nurses but also schoolteachers in her problems which thus were inter preted as functional

For short periods her condition was characterized by drowsiness confusion delusions of influence and visual and auditory hallucinations the latter she did not seem to recognize as true percepts She saw men in black robes and heard them talk to her in deprecatory terms and also occasionally experienced auditory hallucinations hearing music and people talking At school she had repeated faintings which could not be explained by orthostatic hypotension These and her hallucinations were thought to be functional During these years she complained of constant insomnia, and her consumption of sleeping pills steadily increased

At age 19 years she was brought to a psychiatric clinic for adults During the next two years she was treated *there as in patient on six occasions Some of the visits* were caused by suicide attempts and depression was con stant but of varying degree She again claimed to be hear ing voices of the men in black robes telling her that she had no right to live moreover she repeatedly reported extreme exhaustion and depressive delusions The disease pattern was regarded as a mixed sensitive-depressive picture with syntonic hallucinations and delusions It was possible to objectivize her insomnia which even large doses of hypnotic medications could not correct

This young woman thus presented a psychiatric picture that could not be placed in any of the commonly accepted psychiatric nosological categories Nor has her experience and behaviour provided any strong support for the suspi cion of schizophrenia which diagnosis was a guideline for the therapeutic endeavours for about one year when she was receiving large doses of phenothiazines However this therapy besides psychostimulating drugs psycho-therapy tricyclic antidepressants and electroconvulsive shock therapy proved ineffective

When the patient was aged 25 years a new therapeutic approach seemed justified In view of recent reports on the effectiveness of combined administration of tricyclic antidepressants and thyroid hormones this combination was tried She was given imipramine and triiodothyronine This produced dramatic results her depression resolved her insomnia ceased and she rapidly gained a normal psychic and physical capacity Imipramine was later with drawn without recurrence of depressive symptoms For two years this favourable state has been maintained She has completed her education has been working as a *schoolteacher for six months and has recently married* However during the investigations described below she received no triiodothyronine medication and she again became depressed until thyroid substitution therapy was reintroduced

INVESTIGATIONS

EEG taken when the patient was aged 11 years showed a focal theta abnormality corresponding to the right parietal lobe EEG registrations six and ten years later were normal

Psychometric investigations at age 11 and 21 gave find ings compatible with depression but no indications of schizophrenia

A somatic examination with organic illness in mind was undertaken when she was 25 Cutis and body hair were normal and there was no hoarseness The thyroid gland was of normal size There was no macroglossia The heart was not enlarged and the heart sounds were normal There was no bradycardia No edema was found A neurological examination was also normal Her bowel habits and menstruations were reported normal and a gynecological examination was negative Routine chemi cal and morphological examinations of blood and urine including serum cholesterol were unremarkable

The protein-bound iodine was repeatedly found to be low or within the lower normal range 3 5 µg/100 ml before treatment and 3 6 µg/100 ml after a 10-day with drawal of the treatment The T_3 resin uptake was 109%

and 89% respectively The thyroid 24-hour uptake of radioactive iodine was considered normal (37%) Repeated analyses of cholesterol and triglycerides gave normal results No thyroid autoantibodies could be demonstrated Ten days after withdrawal of triiodothyronine a TRF loading was done TSH was estimated 10 min before and immediately before an i v injection of a loading dose of 0 1 mg TRF The values found were less than 3 and 7 μU/l respectively and the loading dose did not cause any significant elevation of the serum TSH (Fig 1) TRF was supplied by Hoffmann-La Roche

DISCUSSION

In 1969 Prange (12) reported a potentiating effect of triiodothyronine on imipramine in treating depressions This treatment was based on the observation that the toxicity of imipramine was accentuated when given to hyperthyroid subjects The findings by Prange were later confirmed by Wheatley (15)

In recent years a possible connection between depression and the hypothalamic pituitary thyroid axis has been discussed In 1972 Prange et al (13) registered a short lasting but prompt therapeutic effect on depressive symptoms after i v administration of TRF to depressed patients with normal thyroid and pituitary function Mountjoy et al (10) reported a series of depressed patients treated with orally administered TRF However neither in this study nor in the study by Hall et al (6) who used TRF i v could any effect be discerned Hutton (8) commented on his reluctance to entirely dismiss a neuro-endocrinological hypothesis as some of the patients apparently had a defect in the hypothalamic pituitary system demonstrable at TRF loading Although Coppen et al (3) were unable to demonstrate any therapeutic effect of i v TRF in a double blind cross-over study some of their patients unquestionably had a pituitary TSH release defect documented by a pathological response to TRF loading

Selective pituitary deficiency of TSH used to be regarded as rare but the recent availability of TRF for routine clinical testing might cast doubt on this The following evidence favours the diagnosis of a selective TSH deficiency in our patient absence of response to TRF loading prompt response to treatment with triiodothyronine later replaced by levothyroxin relapse with severe depressive symptoms after withdrawal of the triiodothyronine treatment and disappearance of symptoms after reinstitution of therapy The diagnosis is further supported by the fact that this patient who had a severe psychiatric disease for 16 years has been followed for more than two years on thyroid substitution therapy during which period she has remained symptom free It is tempting to speculate on the relevance of the cerebral dysfunction which manifested in focal EEG abnormalities demonstrated before her psychiatric illness Theta abnormalities in rheumatic fever have been described by Nyman (11) to quote his report general and local changes in the brain often form part of the acute rheumatic process even without a clinical picture of rheumatic brain disease or chorea

The psychiatric illness of our patient agrees with Asher s (1) and Easson s (5) descriptions of psychotic manifestations in hypothyreosis It is impossible to judge the extent to which her disease also agrees with that of the depressed patients with defective TSH release on TRF loading described by Coppen et al (3) as these authors gave no detailed clinical descriptions

In conclusion we believe that some patients with depressive illness might have a defective TSH release on TRF loading even if evidence of clinical thyroid disease is absent and that these patients some of whom might present a clinical picture compatible with classical descriptions of myxedematous madness might markedly benefit from thyroid replacement therapy A similar line of thought has been proposed very recently by Puhringer et al (14) who maintain that TRF might be useful not for antidepressant therapy but as a screening test for the identification of a possible biochemically distinct subgroup of affective disorders

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A Nitrofurantoin-induced Disorder Simulating Chronic Active Hepatitis

A Case Report

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ABSTRACT A 78 year-old woman with liver damage resembling chronic active hepatitis and occurring during long term nitrofurantoin treatment is described On admission to hospital she displayed jaundice, ascites and high serum levels of GOT, GPT, bilirubin and γ-globulin as well as high titres of ANF and antibodies against smooth muscle cells After withdrawal of nitrofurantoin the clinical and laboratory picture normalized without corticosteroid treatment, suggesting that the liver reaction was drug induced

Nitrofurantoin induced pulmonary reactions of both an acute and a chronic type are well documented in the literature (4 9 12 13) Other nitrofurantoin induced manifestations of disease such as a lupus like syndrome have been described (2 11) Several cases of hepatic disorders such as toxic hepatitis and intrahepatic cholestasis have also been reported in connection with nitrofurantoin medication (1 3 5 7) Hepatic reaction of an autoimmune type seems however to have been discussed in only a few cases (2 6 11)

The following case report describes a patient who developed a hepatic disorder simulating chronic active hepatitis during long term treatment with nitrofurantoin

CASE REPORT

The patient a 78 year-old female was admitted to Serafimerlasarettet on May 29 1973 for evaluation of greatly increased SGOT and SGPT levels

In 1945 and 1950 benign subcutaneous tumors had been extirpated from her breasts In 1966 a right sided radical mastectomy had been performed because of a cancer At a check-up 3 years later in 1969 a marked anaemia was noticed and the patient received blood transfusions at another hospital Haemolysis and kidney dysfunction occurred in connection with this episode Coombs test was negative No explanation for this haemolytic attack was obtained The renal function practically normalized within 1 month (serum creatinine=1 4 mg/100 ml) Six months later her serum creatinine level was normal and has remained so until the time of writing

During follow-up over the next four years she had repeated urinary tract infections She was treated intermittently with nitrofurantoin 50 mg 2–3 times daily from April 1969 to Feb 1972 from April 1972 to June 1973 she *received nitrofurantoin constantly 50 mg 1–3 times daily*

In April 1973 the patient complained of discomfort She lost about 7–8 kg in weight over the next two months and her appetite declined successively Laboratory tests showed a marked increase in SGOT and SGPT (Fig 1)

On admission to Serafimerlasarettet on May 29 1973 the patient showed slight pitting oedema of the lower leg without other signs of heart failure She was slightly icteric The liver was palpable 7 cm below the right costal margin in the medioclavicular line No other pathological masses were found in the abdomen There was a moderate ascites *The levels of SGOT SGPT and bilirubin were* markedly elevated (Table I and Fig 1) The prothrombin time was low (25%) Paper electrophoresis of serum showed reduced albumin and an increased polyclonal γ-globulin fraction Au antigen test was negative No increase was observed in serum alkaline phosphatases numbers of leucocytes or eosinophils Chest X ray was normal

During the first five days in hospital the levels of SGOT SGPT and bilirubin increased further The nitrofurantoin medication was immediately withdrawn During the next two months SGOT SGPT and bilirubin slowly normalized (Fig 1) The patient received spironolactone 25 mg four times daily which resulted in weight reduction from 86 6 to 77 7 kg within a fortnight She also received multivitamins during the hospital stay No corticosteroid treatment was given

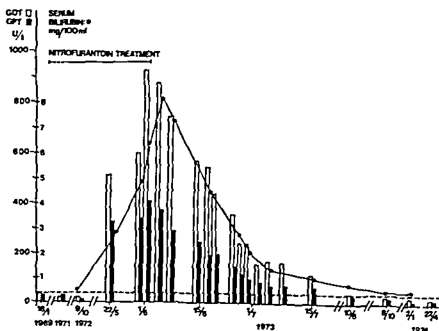


Fig 1 Serum levels of bilirubin GOT and GPT ---- = upper normal limits of GOT and GPT

On admission the antinuclear factor (ANF) titre was 1/100 increasing to ≥1/1 600 a fortnight later At this time *antibodies against smooth muscle cells were found in an* elevated titre of 1/100 The C3 and C4 complement levels were normal The titres of ANF and smooth muscle antibodies decreased slowly and had normalized by Aug 1974 (Table I) At this time the previously greatly increased γ-globulin fraction had normalized Earlier signs of liver dysfunction such as low serum albumin and low prothrombin levels were also restored A galactose loading test in May 1974 was normal ($T\frac{1}{2}$=11 5 min normal <17 min)

Histological examination of a liver biopsy specimen in 1973 (performed by H Nordenstam M D) revealed fibrosis mainly in the portal zones Most liver damaged and cell necrosis was observed in parts of the specimen A marked inflammatory reaction with mostly polynuclear leucocytes was found in the portal zones without signs of cholestasis A new liver biopsy in June 1974 showed that the histological picture had greatly improved Signs of only mild fibrosis were seen The earlier observation of cell necrosis and inflammatory reaction had disappeared

After two months the patient could be discharged from hospital subjectively and objectively improved Spironolactone treatment in a reduced dosage was continued for six months Since then she has been clinically well without medication At the last examination in Jan 1975 all laboratory tests were normal

DISCUSSION

Many drugs are known to induce liver damage Most of these reactions seem to be of a toxic or cholestatic type During the recent 15 years such reactions have also been reported in connection with nitrofurantoin treatment (1, 3 5 7)

In 1973 Lamberger and v Schenk (6) described a patient with liver damage without cholestasis but

Table I *Some relevant laboratory findings before during and after nitrofurantoin treatment*

	1969	June 73	July 73	Aug 73	Jan 74	Aug 74
Nitrofurantoin medication	*No*	*Yes*	*No*	*No*	*No*	*No*
Albumin (g/l)	–	21	21	28	–	41
γ-globulin (g/l)	–	40	36	33	–	14
Simplastin-A (%) (prothrombin)	100	22	32	–	96	–
ANF titre	–	≥1/1 600	–	≥1/1 600	1/100	1/25
Smooth muscle antibodies titre	–	1/100	–	1/25	Neg	Neg
SGOT (U/l) (normal 35)	*14*	*930*	*169*	*41*	20	19

with an increase in the IgG fraction of the serum However this patient had received both poly thiazide and nitrofurantoin

To our knowledge three patients have been reported in the literature who during long term treatment with nitrofurantoin have presented a laboratory picture similar to that described in chronic active hepatitis (2 11) These patients however also exhibited a lupus like syndrome including pulmonary fibrosis The liver reaction in our case was the same as that described in these three patients and simulated the clinical and laboratory picture of chronic active hepatitis Thus high levels of SGOT SGPT and γ globulin as well as high titres of ANF and antibodies against smooth muscle cells were observed but our patient exhibited no pulmonary involvement Similar reactions have been described in patients treated with other drugs e g oxyphenisatin chlorpromazine and sulphonamides (8 10 14)

In several cases of nitrofurantoin induced pulmonary fibrosis an increased titre of ANF has been reported as well as a lupus like syndrome Consequently long term treatment with nitrofurantoin might cause tissue damage through an immunological reaction This theory is strengthened by the fact that lymphocytes from such patients can be stimulated by nitrofurantoin in a lymphocyte transformation test (2)

The present patient had only been treated with nitrofurantoin in the year before liver disease appeared indicating that nitrofurantoin is the most likely cause of the liver damage Support for this possible connection might have been obtained by a provocation test but this was considered unethical in view of the severe initial liver reaction

It is concluded that drug reactions should be considered among the aetiological factors of chronic active hepatitis and that nitrofurantoin administration should be avoided in such cases

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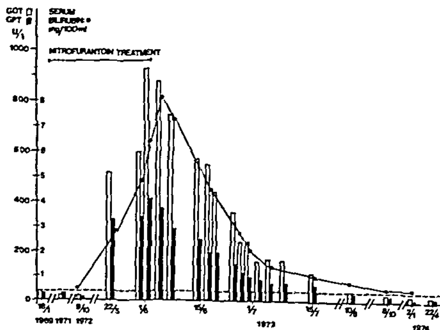


Fig 1 Serum levels of bilirubin GOT and GPT = upper normal limits of GOT and GPT

On admission the antinuclear factor (ANF) titre was 1/100 increasing to ≥1/1600 a fortnight later At this time antibodies against smooth muscle cells were found in an elevated titre of 1/100 The C3 and C4 complement levels were normal The titres of ANF and smooth muscle antibodies decreased slowly and had normalized by Aug 1974 (Table I) At this time the previously greatly increased γ-globulin fraction had normalized Earlier signs of liver dysfunction such as low serum albumin and low prothrombin levels were also restored A galactose loading test in May 1974 was normal ($T\frac{1}{2}$=11 5 min normal <17 min)

Histological examination of a liver biopsy specimen in 1973 (performed by H Nordenstam M D) revealed fibrosis mainly in the portal zones Most liver seemed damaged and cell necrosis was observed in several parts of the specimen A marked inflammatory reaction with mostly polynuclear leucocytes was found in the portal zones without signs of cholestasis A new liver biopsy in June 1974 showed that the histological picture had greatly improved Signs of only mild fibrosis were seen The earlier observation of cell necrosis and inflammatory reaction had disappeared

After two months the patient could be discharged from hospital subjectively and objectively improved Spironolactone treatment in a reduced dosage was continued for six months Since then she has been clinically well without medication At the last examination in Jan 1975 all laboratory tests were normal

DISCUSSION

Many drugs are known to induce liver damage Most of these reactions seem to be of a toxic or cholestatic type During the recent 15 years such reactions have also been reported in connection with nitrofurantoin treatment (1 3 5 7)

In 1973 Lamberger and v Schenk (6) described a patient with liver damage without cholestasis but

Table I *Some relevant laboratory findings before during and after nitrofurantoin treatment*

	1969	June 73	July 73	Aug. 73	Jan. 74	Aug 74
Nitrofurantoin medication	No	Yes	No	No	No	No
Albumin (g/l)	–	21	21	28	–	41
γ-globulin (g/l)	–	40	36	33	–	14
Simplastin-A (%) (prothrombin)	100	22	32	–	96	–
ANF titre	–	≥1/1600	–	≥1/1600	1/100	1/25
Smooth muscle antibodies titre	–	1/100	–	1/25	Neg	Neg
SGOT (U/l) (normal 35)	14	930	169	41	20	19

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REVIEW AND REFLECTIONS

Man and Medicine Four numbers yearly of about 300 pages Executive Editor Michael Meyer Columbia University College of Physicians and Surgeons 630 W 168th Street New York N Y 10032 12$/year

The number of new medical journals is increasing steadily pari passu with the tendency towards specialization It is rare however to see a new periodical treating fundamental and general problems such as are defined in the title of the new "Man and Medicine the journal of values and ethics in health care" The US is at present the country where the sociology and philosophy of science including medicine is flourishing It is enough to mention the excellent series of monographs on such problems published under the auspices of the American Academy for Arts and Sciences in Boston with the title Daedalus

"Man and Medicine" has started with a first number of unusual quality The subjects of the papers are varying and there are also excellent commentaries by invited scientists who are partly critical partly reverential In the first case one author has been given an opportunity to formulate a "reply" This organization of the material guarantees a lively presentation of the facts Topics treated are Regulation of genetic engineering one of the hottest in science at the present moment value conflicts regarding abortion with some outstanding commentaries and several other subjects Two of the latter will be discussed at some length here because they have so much importance also for Scandinavian medicine

Doctor Geelhoed is presented as admitting officer at the National Cancer Institute His essay on the conquest of cancer as the Holy Grail of many leaders of medicine and society is admirable when it discusses the many faceted problems with sound scepsis regarding the politicians simple faith that *a cure* for cancer can be bought just like a ticket to *the moon* He also stresses the probability that we shall only obtain piecemeal advances in our knowledge regarding therapy of malignant disease In several papers I have presented exactly the same points One phrase seems to me to be extremely well taken "Concomitant with medical progress civilization must also develop so that medical advances can be tolerated in human society"

It is clear that global ecology—to use the modern must in any front line discussion to-day—has been completely upset by all the great medical advances The more effective the more upsetting are the results The wonderful effects of public health measures in the tropics have brought down infant mortality to such an extent that over population has become one of the great tragedies of our time Nobody would deny that antibiotics have worked wonders and given the doctors weapons to fight some of the most cruel diseases One third of all patients who developed lobar pneumonia in all the countries of the world died in the earlier times The use of antibiotics is no doubt the most important factor accounting for the present day situation in geriatrics with such an accumulation of decrepit old people who are only partly alive Even the wonderful therapeutic triumph insulin has been two-edged in the same sense

In a commentary a professor of Economics at Columbia University who is at present Director Conservation of human resources makes some very pertinent remarks also regarding human experimentation including the fact that patients with malignancies are kept alive with continued expensive and emotionally bordering treatment for the sake of finding new drugs or other forms of therapy The salient question is "would the patient opt for a quicker and quieter death?" The very appropriate question is also raised The present reviewer has always preached the thesis that we as doctors have to recognize when we are beaten by the disease and admit that the final stage of the cancer patients life should no longer be filled with expensive and often painful attempts at *cure* At this moment human *care* is more important Too many cancer patients with no pain are treated relentlessly with chemotherapy and/or radiation even when it is clear that they would be much happier living some

months with their family and only getting palliation —if necessary The old Roman word vixit dum vixit laetus—he lived happy as long (or perhaps as short) as he lived—is usually forgotten by modern technically minded overzealous doctors So much for my own opinions The whole discussion is concerned with a wealth of critical questions Why is it that we don t know anything about the *real* value of treatments that are extremely unpleasant to say the least for the patient and still are used all over the world because they are *believed* to be salutary!

In the present day Swedish discussion about cancer prophylaxis it is interesting to note how quantitatively less important factors get a maximum of publicity for political reasons whereas the mass media avoid propaganda against smoking the real criminal in the cancer drama Prevention in that case is easy treatment is lamentably inefficient

The last lecture is eminently important for a majority of the readers of the Acta Medica It treats the crisis of academic internal medicine in the US and it is remarkable that almost all the important points also are of interest in Scandinavia even if the organization of health delivery both in out patient clinics and in the hospitals is different in many ways The author is one of America s leading professors in medicine Paul Beeson who has a wide experience as he has been head of the department at Yale and also worked as professor for several years in Oxford His remarks on the development of this central subject in the medical curriculum and also on decisions regarding the appropriation of funds for research are well worth a close study The presentation is extremely clear and concise the examples are well chosen and to my mind it must be regarded as a masterpiece

Having said this it is clear that we recommend this new journal unhesitatingly hoping that it will continue to have the same high standards The we is a pluralis majestatis adopted according to a quotation from Mark Twain cited in the new journal Only presidents editors and people with tapeworm are entitled to use the editorial we

Jan G Waldenstrom

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Plasma Renin Activity and Hypertensive Organ Manifestations in 50-year-old Males

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ABSTRACT From a screening examination in a randomly selected third of the 50 year-old male population in Goteborg Sweden a 10% subsample was selected as a reference group ($n=80$) All untreated persons with SBP>175 or DBP>115 mmHg on two separate occasions made up the hypertension group ($n=35$) The reference group and the hypertension group were subjected to the same investigations including BP measurement before and after rest and determination of plasma renin activity (PRA), urinary sodium and norepinephrine excretion and GFR Plasma renin activity was approximately normally distributed in both the reference and the hypertension group Mean values were $0\ 78\pm0\ 18$ and $0\ 65\pm0\ 17$ ng/ml/h respectively the difference being almost statistically significant ($0\ 10>p>0\ 05$) There was no difference with respect to sodium excretion between the reference group and the hypertension group In the reference group, heart rate was positively correlated to PRA and to urinary norepinephrine excretion during the day No linear correlation between PRA and BP was found either in the reference group or in the hypertension group Sodium excretion during the day was positively correlated to GFR in the hypertension group but not in the reference group Compared to hypertensives with normal or high sodium excretion during the day the hypertensives with low sodium excretion during the day were characterized by a higher BP a lower GFR and a reversed diurnal rhythm of urine excretion Thus low sodium excretion seemed to indicate more severe hypertension with increased renal resistance during the day The hypertension group was also divided with regard to sodium excretion into a low normal and high renin group The low renin group had the lowest GFR and with rising renin group (from low via normal to high) there was a significant increase in GFR and a significant decrease in resting BP The results indicate that low renin hypertension is not a more mild but indeed rather a more severe form of hypertension

The role of sodium balance and plasma renin activity (PRA) in the development of essential hypertension and hypertensive organ manifestations has been debated intensely in recent years Studies in benign essential hypertension have shown high as well as normal and low PRA within the hypertensive population (15 17 18 22) Laragh and co-workers (5 6 20 21) have presented a theoretical model founded on several studies according to which the hypertensive population can be divided into three PRA groups with regard to the sodium balance Those with low PRA would be characterized by an increase of the plasma volume and the extracellular volume lower peripheral resistance and better organ perfusion (16 17) The high renin group on the other hand would be characterized by strong vasoconstriction a small plasma volume high peripheral resistance and a less open microcirculation Hypertensive subjects with low PRA have been claimed to have more benign hypertension with a lower prevalence of myocardial infarction and stroke (5 6) The same authors also found a more severe hypertension with increasing PRA as judged from BP and kidney function Other authors however have not been able to verify these findings (1 9 25) The suggested disease entity of low renin hypertension has recently been reviewed (10)

Other results are in direct contrast to these findings Thus Schalekamp et al (28) found that low PRA was associated with high renal and peripheral resistance low renal blood flow and a high filtration fraction The results were interpreted as a fall of PRA with increasing renal resistance in patients with more severe hypertension The fall of PRA would be mediated through the increased pressure in the afferent (preglomerular) arterioles in ac

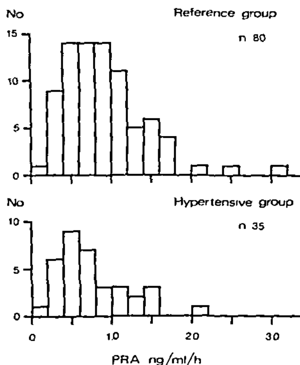


Fig 1 PRA in the reference group and in the hyper tension group

cordance with the baroreceptor hypothesis of renin release (7) All the studies mentioned have been performed in selected groups mostly collected in hospitals Studies of PRA in age and sex homo geneous groups of normo- and hypertensives have not been published

This paper presents results of determinations of PRA glomerular filtration rate (GFR) urinary um and norepinephrine excretion and non asive examinations of the heart function in 50 -old normo- and hypertensive males The aims of this study were to determine whether differences in PRA and urinary sodium excretion could be found between normotensives and hypertensives and to study the relationship between these two variables and blood pressure (BP) heart rate (HR) urinary norepinephrine excretion and renal func tion Another objective was to investigate whether the previous finding of high renin hypertension as a more severe form of hypertension could be verified in this randomly selected series

MATERIAL AND PROCEDURE

Both the material and the procedure of the investigations have been previously described (3) Briefly a 10% sub-sample of the 50-year-old male population in Goteborg Sweden was randomly selected as a reference group (n=80) All subjects without antihypertensive treatment and with SBP>175 or DBP>115 mmHg on two separate occasions made up the untreated hypertension group (n=35) Subjects on antihypertensive treatment at the screening examination were included in the treated hyper tension group (n=22) The present communication is based only on untreated hypertensives as significant dif ferences in BP and PRA were found between the untreated and treated hypertensives

METHODS

The methods for measurement of BP and HR height weight and relative body weight GFR urine volume urinary sodium excretion and creatinine concentration chest X ray and statistical methods have been described previously (3)

Plasma renin activity

No dietary salt instructions were given for the days pre ceding the investigation Venous blood samples for PRA determinations were drawn at 8 a m after 10 min supine rest PRA was determined according to Giese et al (13) In this method the plasma sample is dialysed prior to incubation to assure efficient inactivation of angio-tensinases The generated angiotensin I is extracted from the incubate and estimated by radioimmunoassay Based on a series of 20 double determinations the error of a single PRA measurement was calculated to be 14% of the mean value

Urinary norepinephrine determinations

The urinary norepinephrine excretion was determined separately for the day and the night A modified method according to von Euler and Floding (11) only measuring free norepinephrine was used Subjects who were sus pected of inadequate urine collection were as previously described excluded from the analysis (3)

Non invasive methods for determination of cardiac function

Orthogonal and conventional 12 lead ECG were recorded in all participants while apexcardiography and phono-cardiography were done in randomly selected halves of the reference and the hypertension groups The methods have been described in detail elsewhere (30) High R waves ($R > 1.8$ $R > 1.3$ or $R_x+S_y>1.9$ mV) or LV con duction disturbances (left bundle branch block or left anterior hemiblock) on orthogonal ECG were taken as electrophysiological signs of left ventricular involvement as these criteria together were the best discriminators of left ventricular involvement between the hypertension and the reference group

RESULTS

Plasma renin activity

Both in the reference and in the hypertension groups PRA was roughly normally distributed with a slight skew to the right (Fig 1) Mean values

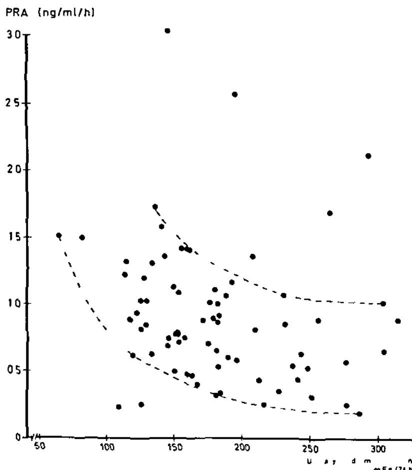


Fig 2 PRA and urinary sodium excretion in the reference group

were 0.78 ± 0.18 and 0.65 ± 0.17 *ng/ml/h* respectively the difference being almost statistically significant ($0.10 > p > 0.05$)

In the reference group HR after rest was positively correlated to PRA ($r = 0.37$ $p < 0.05$) The corresponding r in the hypertension group was 0.22 (n s)

No significant correlations were found between PRA and BP urine volume creatinine concentration urinary sodium ad norepinephrine excretion during the day or night or GFR either in the reference or in the hypertension group There was no difference in PRA between hypertensives belonging to WHO stages 1 ($n = 18$) 2 ($n = 13$) and 3 ($n = 4$) No differences were found between three subgroups (tertiles $n = 13$ 11 11) with low (<0.50) medium (0.51–0.87) and high PRA (>0.87 ng/ml/h) with regard to BP before and after rest GFR or in prevalence of electrophysiological signs of left ventricular involvement and decreased distensibility of the left ventricle

Urinary sodium excretion

There was no difference in sodium excretion between the reference group ($\bar{x} = 181 \pm 55.4$ mEq/24 h) and the hypertension group ($\bar{x} = 169 \pm 54.8$ mEq/24 h) In the reference group urinary sodium excretion during the day correlated significantly and positively to urine volume and negatively to urinary creatinine concentration during the day There was no correlation between urinary sodium excretion and BP before or after rest GFR or PRA In the hypertension group urinary sodium excretion during the day was positively correlated to urine volume during the day ($r = 0.44$ $p < 0.01$) GFR ($r = 0.43$ $p < 0.05$) and urinary norepinephrine excretion ($r = 0.46$ $p < 0.01$) BP before and after rest was highest in the group with the lowest urinary sodium excretion Subjects with the lowest urinary sodium excretion had a tendency towards a reversed diurnal rhythm of urine excretion with less but more concentrated urine during the day However these differences were not statistically significant

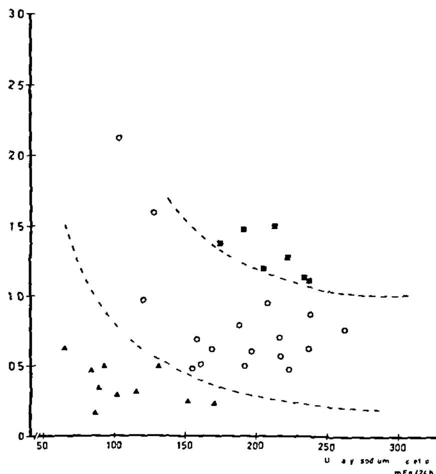


Fig 3 PRA and urinary sodium excretion in the hypertension group The limits from Fig 2 are drawn and divide the subjects into those with low (▲) normal (○) and high PRA (■)

Urinary norepinephrine excretion

There were no differences in mean values between hypertension and reference group In the reference group HR at rest was positively correlated to urinary norepinephrine excretion during the day ($r=0.42$ $p<0.05$) Linear regression analysis in the reference and hypertension groups showed no significant correlation between urinary norepinephrine excretion during the day or night and PRA

Low normal and high PRA with regard to sodium excretion

In order to analyse whether hypertensives with high PRA with regard to sodium excretion had a more severe hypertension an analysis was applied which followed previous studies (5 6) as closely as possible In analogy with these studies arbitrary limits between low normal and high PRA with regard to sodium excretion were drawn in the reference group as shown in Fig 2 Sixty six of 72 subjects (90%) fell within these limits Two subjects fell below the lower limit one had a chronic glomerulonephritis and both had relatively high screening BP (164/122 and 172/96 mmHg respectively) and low GFR (62 and 80 ml/min respectively)

Fig 3 shows the relationship between PRA and sodium excretion in the hypertension group The limits from Fig 2 are projected and divide the group into those with low (10/34=29%) normal (17/34=50%) and high renin (7/34=21%)

Table 1 shows that GFR was lowest in the low renin group and highest in the high renin group ($p<0.05$) SBP and DBP were highest in the low renin group and lowest in the high renin group ($p<0.05$) Although not statistically significant there was a tendency towards lower BP before rest from the low renin group to the high renin group and urinary norepinephrine excretion tended to rise between the same groups Furthermore those with low renin with regard to sodium excretion had a reversed diurnal rhythm of urine ex

Table I *Results in three subgroups of the hypertension group with low, normal and high PRA with regard to sodium excretion*

	Low PRA			Normal PRA			High PRA		
	n	*x*	s_x	*n*	*x*	s_x	*n*	*x*	s_x
SBP (mmHg)									
Before rest	10	202	15.2	17	197	13.4	7	193	18.3
After rest	4	173	4.1	10	155	24.0	5	137	20.5
DBP (mmHg)									
Before rest	10	121	8.9	17	118	10.4	7	111	9.0
After rest	4	108	8.2	10	95	14.5	5	85	13.7
Norepinephrine excretion (μg/12 h)									
Day	10	28	15.4	17	31	10.0	7	37	9.2
Night	10	14	3.3	17	18	7.3	7	18	4.4
Day + night	10	42	17.6	17	48	14.4	7	56	10.7
Urine volume (l)									
Day	10	0.64	0.24	17	0.77	0.18	7	0.77	0.17
Night	10	0.71	0.29	17	0.74	0.23	7	0.73	0.26
Creatinine concentration (mg/l)									
Day	10	1 400	500	17	1 230	411	7	1 180	5 0
Night	10	1 240	610	17	1 170	460	7	1 180	470
Sodium excretion (mEq/12 h)									
Day	10	49	12.6	17	97	30.9	7	109	23.6
Night	10	60	27.2	17	89	26.9	7	102	16.9
Day + night	10	109	33.3	17	187	45.0	7	211	23.2
GFR (ml/min/1.73 m² BSA)	10	89	15.2	17	96	13.2	6	105	9.6
Heart volume (cm³/m² BSA)	10	419	63.1	17	433	69.6	7	416	43.9
	n	%		*n*	%		*n*	%	
Signs of left ventricular hypertrophy on X-ray	5/10	50		8/17	47		1/7	14	
Electrophysiological signs of heart involvement[a]	6/10	60		7/17	41		1/7	14	
Signs of decreased left ventricular distensibility	2/4	50		5/10	50		2/5	40	

Investigation performed in a randomly selected half of the group.

[a] $R_x > 1.8$, $R > 1.3$ or $R_x + S > 1.9$ mV and/or conduction disturbances (LBBB or LAH) on orthogonal ECG.
a/H ratio > 15% on apexcardiogram and/or pathological fourth heart sound (grade 4–5 on 5 point scale).

cretion, with small volume and high concentration during the day and a low urinary sodium excretion. Those with high renin tended to have a lower frequency of signs of left ventricular hypertrophy on X-ray, of electrophysiological signs of heart involvement and of signs of decreased left ventricular distensibility. None of these differences was statistically significant, however.

DISCUSSION

To our knowledge no previous study of the relationship between PRA and hypertensive organ manifestations has been performed in groups of hypertensives derived from screening of total population samples. The epidemiological method used makes it possible to generalize the results to other populations with a background similar to that of the inhabitants of Göteborg. Furthermore, the studied groups were sex- and age-homogeneous, which suggests that findings might be attributed with greater certainty to the hypertension, as the influence of age and sex on the variables was ruled out. Only untreated hypertensive subjects were included, as the influence of antihypertensive treatment was obvious, despite the fact that treatment was withdrawn one month prior to the investigation. The majority of subjects in the hypertension group had mild hypertension and normalized their BP during prolonged rest.

The reference group constitutes a normal material for 50-year-old white males. The absolute values of PRA in the present study are in good accordance with previous studies in normal subjects using

the same or similar renin assay methods (13 14 29) As has been shown in previous studies (8 24) no difference was seen in mean sodium excretion between the reference group and the hypertension group

The inverse relation between PRA and sodium excretion which has been revealed under carefully standardized conditions (2 5 19) was not observed in this out patient study Determinations were made only once in each subject and urine collection was made on an out patient basis without instructions regarding low salt intake This may explain the discrepancy

A reversed diurnal pattern of salt and water excretion in subjects with more severe essential hypertension which was indicated in the present study has previously been shown to be associated with high renal vascular resistance (4) The present results showing a positive correlation between sodium excretion during the day and GFR in the hypertension group have therefore been interpreted as a parallel fall in these two variables in hypertensive subjects with a high renal resistance during the day

It has been suggested that the higher renal vascular resistance in more severe essential hypertension might be explained by increased sympathetic nervous system activity with renal vasoconstriction during the day and normalization during the night (4) Our finding that hypertensive subjects with signs of increased renal vascular resistance seemed to have a lower urinary norepinephrine excretion 1) does not support this explanation It rather rs the view that a higher renal vascular resistance might be explained on the basis of structural vascular changes with an increased wall/lumen ratio (12) in subjects with more severe essential hypertension

The hypothesis that high PRA with regard to sodium excretion represents a more severe form of hypertension (20 21) was tested in our material by adopting Laragh s method of analysis (5 6) as closely as possible However the procedure for sampling venous blood as well as the method of PRA determination differed between our study and the one cited above so they are not fully comparable Furthermore the question of PRA as a risk factor for the development of myocardial infarction and stroke could not be analyzed in this study because of its cross sectional design and the limited number of hypertensives studied According to our study subjects with low renin hypertension are characterized by higher BP decreased renal function and possibly by more severe heart involvement than other hypertensives Therefore our results suggesting that low renin hypertension is a more severe form of hypertension are at variance with previous studies (5 6) These studies showed significantly higher diastolic BP and higher blood urea nitrogen in hypertensives with high renin while our results suggest that high renin is accompanied by lower BP and higher GFR

Our study is based on screening of a large population which gives the same chance for hypertensives of different severity to be represented The studies of Brunner et al (5 6) seem to be based on selected cases from specialized out patient clinics which might imply an overrepresentation of subjects with severe hypertension and organ damage The discrepancies in results might be explained by differences in the composition of the groups studied Our results are in agreement with those of Mroczek et al (25) de Quattro (27) and Louis (23) All these studies of benign essential hypertension showed a decrease in BP from the low to the high PRA group when low normal and high PRA were defined in relation to the urinary sodium excretion Our interpretation of the physiological mechanisms involved is that the decrease of PRA is merely secondary in more severe hypertension due to an increased renal vascular resistance with increased pressure in the preglomerular arterioli This interpretation is supported by previous studies on the relationship between PRA and renal vascular resistance (28) showing a negative relationship between these two variables Our data support the suggestion that low renin hypertension is rather a stage in the development of essential hypertension than a separate diagnostic entity (26)

ACKNOWLEDGEMENTS

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Hemodynamic Effect of Pindolol in Essential Hypertension with Special Reference to the Resistance and Capacitance Vessels of the Forearm

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ABSTRACT Ten patients mean age 48 years with essential hypertension of stage I and II according to the WHO classification have been studied at rest and during work before and after on average 8 weeks oral treatment with a β-adrenergic blocking agent pindolol The pindolol treatment caused a significant decrease in the systemic systolic and diastolic blood pressure heart rate and cardiac output both at rest and during work The systemic vascular resistance and the forearm vascular resistance decreased significantly after and during work, respectively Forearm venous tone was significantly decreased at rest during and after work The plasma renin activity decreased Three mechanisms seem to be involved in the antihypertensive effect of pindolol 1) a negative chronotropic effect on the heart 2) a decrease in peripheral vascular resistance and 3) an increase in vascular capacitance affecting the venous return

The antihypertensive effect of β adrenergic blocking agents has been documented in a large number of publications (12 17 and others) However the mechanisms by which the blood pressure is decreased are still incompletely elucidated Hemodynamically an elevated arterial BP may be interpreted as the consequence of an increase in the cardiac output or the total peripheral resistance or both While the effects of the β blockers on the heart are well known the effect on the peripheral vessels—both the arteries and especially the veins —is less clear

Acute administration of β blockers elicits a decrease in heart rate and thereby the cardiac output The decreased cardiac output is compensated by an increased peripheral vascular resistance resulting in an unchanged arterial BP (1 8 10 15 and others) The hypotensive effect of β blockers appe gradually and is often reported to take several weeks to reach a maximum (14) The fall in the BP might be explained by a decrease in the total peripheral resistance while the cardiac output remains reduced even after more than 18 months of treatment (19) The mechanism behind such a readjustment of the peripheral resistance is not fully understood Prichard and Gillam (13) postulated a resetting of the baroreceptor sensitivity but this hypothesis has been questioned

Besides propranolol which was the first β blocker to come into widespread clinical use in the treatment of hypertension (12) a great number of β blocking agents have been introduced in the last decade Since some of them have somewhat different quantitative as well as qualitative characteristics from propranolol it is important that they too are subjected to detailed clinical and hemodynamic studies It is important that these studies concern the hemodynamic effect of β blockers after both acute and long term treatment of hypertension

In the present study the hemodynamic effect of pindolol has been investigated in patients with essential hypertension The aim has been to register—in addition to the arterial BP— cardiac output and systemic vascular resistance as well as the effect on blood flow vascular resistance and venous tone of a peripheral vascular area (forearm) Plasma renin activity before and during pindolol administration was studied as well

MATERIAL

The study was undertaken in 10 patients with essential hypertension 5 women and 5 men aged 31–61 years (mean

Table 1 *Central hemodynamics before (B) and after (A) administration of pindolol at rest during and 4 min after exercise*

	Rest		Exercise		4 min after exercise	
	B	A–B	B	A–B	B	A–B
Arterial BP (mmHg)						
Systolic						
Mean	193	−34	229	−47	179	−29
S D	22		21		23	
p	<0 001		<0 001		<0 001	
Diastolic						
Mean	106	19	117	−24	105	−21
S D	14		11		12	
p	<0 001		<0 001		<0 001	
Mean						
Mean	140	−23	159	−29	134	−11
S D	13		14		14	
p	<0 001		<0 001		<0 001	
Heart rate (beats/min)						
Mean	74	−8	119	−18	84	−9
S D	12		20		14	
p	<0 01		<0 01		<0 05	
Cardiac output (l/min)						
Mean	5 5	−0 7	10 4	−1 4	6 1	−0 3
S D	1 3		2 5		1 2	
p	<0 05		<0 001		ns	
Stroke volume (ml)						
Mean	75	1	89	±0	76	2
S D	17		21		16	
p	ns		ns		ns	
stemic vascular resistance (arb U)						
an	27	2	16	−1	23	−3
D	8		5		5	
	ns		ns		<0 05	

ns=not significant

The criterion for inclusion in the study was the presence of stage I or II hypertension according to the WHO classification Patients with substantial disorders in addition to hypertension were excluded Examples of such disorders are latent or manifest cardiac insufficiency bronchial asthma renal insufficiency and diabetes No signs of organic cardiovascular changes were present in eight of the patients (stage I according to WHO) the other two had a slightly enlarged heart volume at X ray examination but no other signs of cardiovascular changes (stage II)

Clinical investigation At the start of the study none of the patients had any hypotensive treatment Two patients had discontinued the treatment during the past 2 and 5 months respectively and the hypertension of the remaining eight had recently been discovered All patients underwent a clinical examination including X rays of heart and lungs urography examination of the eye fundi and a work test on a bicycle ergometer with ECG recording One or if possible two work loads were tried out individually on the bicycle ergometer so that the patient would be able to manage the load for 10 min in the supine position during the subsequent hemodynamic study

In order to confirm the diagnosis of hypertension in the individual case initial BP measurements were made (with a cuff and Hg manometer) on three occasions separated by intervals of about one week invariably in the left arm after 5 min rest in the supine position During a subsequent run in period with placebo treatment BP was registered after 2 and 4 weeks

The placebo period ended with a hemodynamic examination at rest and during exercise following the model described below under Methods and procedure After this examination treatment with pindolol was started with a dose of 10 mg twice daily The BP was checked after 1 and 3 weeks of treatment if the diastolic pressure had not fallen at least 20 mmHg or if the BP exceeded 160/95 the dose was increased to 15 mg twice daily After treatment with the higher dose for a further 3 weeks the dose was increased to 20 mg twice daily if the BP had not fallen as indicated above This was the highest dose used When the BP had fallen in accordance with the criterion above the hemodynamic examination was repeated after a further 2 weeks treatment using the same procedure as at the end of the placebo period If the BP did not fall as intended the hemodynamic examination was repeated after treatment with 20 mg pindolol twice daily for 4 weeks Plasma renin activity (PRA i e angiotensin I) was determined during the placebo period and towards the end of treatment with pindolol Samples for this purpose were taken in the morning before the patient got out of bed PRA determinations were also made at rest and immediately after exercise in the hemodynamic study

METHODS AND PROCEDURE

The studies of the central and peripheral circulation were performed in the morning The patient had taken the pindolol dosage 2 hours before the examination but had otherwise fasted for 14 hours Teflon catheters were inserted percutaneously into a brachial artery and the antecubital veins in both arms The right venous catheter was introduced proximally 30 cm and used for dye injections A deep vein was catheterized on the left arm in the antecubital fossa and the catheter inserted 5–7 cm in the distal direction After placement of the catheters and cuffs for plethysmographic recordings the subject rested for about 15 min Cardiac output arterial and venous BPs and forearm blood flow were then determined at rest The patient thereafter exercised on a bicycle ergometer (Siemens Elema Stockholm) in the supine position The work load chosen was 15–50 W (mean 35) If the heart rate reaction to exercise was less than 110 beats/min the load was increased to 80–100 W The duration of exercise was 10 min at each load Cardiac output BPs and forearm blood flow were recorded during the 5th and the 10th min at each load and repeated during the 2nd–4th min at rest after work

Arterial blood for analyses of renin was taken before and 1 min after exercise The procedure was identical in the studies before and during treatment with pindolol

Table II *Peripheral circulatory data at rest during and after exercise before (B) and after (A) administration of pindolol*

	Rest		Exercise		4 min after exercise	
	B	A–B	B	A–B	B	A–B
Forearm blood flow (ml×100 ⁻¹ml×min ⁻¹)						
Mean	2 8	0 1	2 8	−0 2	3 6	±0 0
S D	1 2		1 2		1 7	
p	ns		ns		ns	
Forearm vascular resistance (arb U)						
Mean	60	−14	65	−14	45	−10
S D	28		27		21	
p	ns		<0 05		ns	
Venous tone (mmHg×ml ⁻¹×100 ml)						
Mean	3 0	−1 0	2 9	−0 8	3 3	−1 5
S D	2 0		1 3		2 3	
p	<0 05		<0 01		<0 05	

ns=not significant

Cardiac output was determined by the dye dilution technique using indocyanine green (Cardio-green Hynson Westcott and Dunning USA) as indicator injected into a central vein The concentration of dye was recorded on a cuvette densitometer (Beckman Instr Palo Alto Calif) BPs were recorded with pressure transducers (EMT 34,35 Siemens Elema) and recorded on a direct writing ink jet recorder (Mingograf 81 Siemens Elema) Heart rate was calculated from the ECG Forearm blood flow was measured by venous occlusion plethysmography using the technique described by Dohn (5) as modified by Graf and Westersten (7) Changes in the left forearm volume were recorded with a 5 cm wide thin walled rubber cuff placed around the mid forearm The collection cuff placed around the upper arm was inflated to 40 mmHg The circulation of the hand was excluded by a third cuff placed around the wrist and inflated to 250 mmHg during the flow recordings

Forearm venous pressure was measured through the catheter placed in a deep vein in the left forearm The forearm was placed in a position giving an initial venous pressure close to zero

Systemic vascular resistance was calculated as the ratio of mean brachial artery pressure to cardiac output and expressed in arbitrary units

Forearm vascular resistance was calculated as the ratio of mean brachial artery BP to forearm blood flow

Venous tone of the forearm was defined according to Sharpey Schafer (18) as the ratio of pressure increase ($\Delta P/\Delta T$) to volume increase ($\Delta V/\Delta T$) and expressed as mmHg×ml ⁻¹×100 ml tissue

PRA was analysed in duplicate by radioimmunoassay using the angiotensin kit prepared by Schwartz/Mann Orangeburg NY USA The error of duplicate analyses was 6%

The results are presented as mean values ±S D Student s *t* test was used for the statistical evaluations

RESULTS

The principle for the pindolol dosage in the individual cases is described above under Clinical investigation The final daily dosage of pindolol was in one patient 20 mg in four 30 mg and in five 40 mg daily The mean duration of treatment before the second circulatory study was 8 weeks One of the patients had slight symptoms of insomnia during the first month of pindolol treatment No other side effect appeared Serum creatinine GOT GPT electrolytes WBC RBC and thrombocytes were found to be unaffected by the pindolol treatment

A decrease in *systemic arterial systolic diastolic and mean BP* in connection with pindolol administration was obtained in all patients except one (Table I) The exception was a 59 year-old female with an initial arterial BP of 192/94 (mean 130) increasing during exercise to 220/108 (mean 157) Almost identical values were recorded when the study was repeated during pindolol administration (198/92 mean 135 at rest and 225/98 mean 155 during exercise) *Heart rate* was significantly lower during pindolol administration at rest and during exercise ($p<0.01$) and *cardiac output* was likewise lower at rest ($p<0.05$) and during exercise ($p<0.001$) *Stroke volume* did not change after the administration of pindolol *Systemic vascular resistance* was somewhat lower during pindolol but the difference was significant only after exercise ($p<0.05$) *Forearm blood flow* (Table II) was not affected by pindolol administration *Forearm vascular resistance* at rest and after exercise was lower during pindolol in 6 patients During exercise 8 patients showed lower forearm vascular resistance during pindolol than in the control study The difference was significant for the whole group only during exercise ($p<0.05$) *Venous tone* of the forearm was significantly lower after pindolol administration at rest ($p<0.05$) as well as during ($p<0.01$) and after exercise ($p<0.05$)

Plasma renin activity The basal PRA obtained in the morning before leaving bed was within the normal range in all patients (Table III) PRA analyzed in connection with the hemodynamic study was significantly higher than that found at rest after a night s sleep Supine exercise however elicited no significant change Lower PRA was obtained in all patients in connection with the administration of pindolol

In the patient in whom no hypotensive effect was recorded with pindolol the following additional

Table III *Plasma renin activity (ng×100 ml^{-1} ×h^{-1}) before and during administration of pindolol (mean ±S D)*

	Control value	During pindolol	p
At rest	0 98±0 82	0 26±0 28	<0 01
In connection with the hemodynamic study			
Before exercise	1 85±1 02	0 55±0 33	<0 001
1 min after exercise	1 96±1 49	0 80±0 54	<0 001

data were obtained heart rate was unchanged at rest but decreased during exercise cardiac output did not change forearm blood flow increased at rest but was unchanged during exercise and venous tone was slightly decreased PRA at rest was 1 25 ng× 100 ml^{-1}×h^{-1} before and 0 27 ng×100 ml^{-1}×h^{-1} during pindolol administration indicating that the patient had in fact taken her medication

DISCUSSION

The majority of studies on the antihypertensive effect of β adrenergic blocking agents deal merely with the situation at rest Analysis of the central and peripheral circulation during and after exercise can be expected to add valuable information concerning the effect of the antihypertensive treatment It seems important to determine whether for instance the hypotensive effect obtained at rest is ained during a physical work similar to what patient undertakes in daily life As is evident the present study the effect of pindolol was even more pronounced during exercise than at rest for some of the variables studied such as heart rate cardiac output arterial BP and vascular resistance of the forearm

Similar results were obtained in an acute study on the effect of propranolol and alprenolol (10) where a reduction of arterial BP and cardiac output was observed both at rest and during exercise The decrease in arterial systolic and diastolic BP observed after two months of pindolol administration seems mainly to be due to a reduction in cardiac output as a consequence of the induced bradycardia which confirms earlier findings (6 8) To some extent however the fall in BP in the present study might be due to a change also in the systemic vascular resistance which was lower during pindolol administration the difference however being significant only after exercise This is in accordance with the results of Tarazi and Dustan (19) who pointed out that the total peripheral resistance may fall below the initial level during chronic therapy Also Sannerstedt et al (16) found that four weeks of treatment with a β blocking agent (alprenolol) induced a decrease in systemic vascular resistance both before during and after exercise

Venous tone of the deep forearm defined according to Sharpey Schafer (18) was significantly lower during pindolol administration as compared to the control situation This finding is of interest in connection with an observation by Walsh et al (22) of a reduced venous distensibility in hypertensive patients compared to normotensive subjects Treatment with various antihypertensive drugs such as chlorothiazides reserpine and methyldopa gave an increase in venous distensibility These results seem to indicate an increased sympathetic venomotor activity in hypertensive patients In normal individuals a reflex constriction of the veins mediated by the sympathetic nerves has been demonstrated in normotensive man in connection with deep breathing exercise and other procedures (15 23) Furthermore venous tone is increased by infusion of sympathomimetic amines (4 21) In this connection it is also of interest to note that a shift of the venous pressure–volume curve towards the pressure axis occurs in early experimental renal hypertension in the dog indicating a reduction in venous compliance (11)

Evidently both β and α receptors are present in the venous wall Burcher et al (2) showed that the relaxation of isolated human veins produced by isoproterenol was antagonized by pindolol indicating the existence of β adrenoreceptors Adrenergic nerve stimulation increases the tension of the venous wall and this effect is mediated by α receptors (9) An increased venomotor activity in hypertensive patients postulated by Walsh et al (22) is therefore most likely an α adrenergic effect In the present study both calculated systemic and forearm vascular resistances were reduced by pindolol in most patients both at rest and during exercise although the differences were significant for the whole material only concerning systemic vascular resistance after work and concerning forearm vascular resistance during work Furthermore the venous tone was significantly reduced However no basis for an α adrenergic blocking action of pindolol has hitherto been demonstrated and the

mechanism by which pindolol decreases the venous tone in patients with essential hypertension as shown in this paper is not clear The effect might be an expression of the intrinsic activity of pindolol or an effect on the central nervous system

The part played by the renin–hypertensin system in hypertension has attracted growing attention in recent years both as a conceivable etiological factor and as a guide to the choice of therapy (3) We therefore considered it important to include a PRA analysis in the present study The results show that treatment with pindolol induced a significant reduction of PRA both at rest and in connection with exercise It is however doubtful if any conclusion can be drawn concerning causality between the decrease in PRA and the hemodynamic changes In the patient mentioned earlier in whom no hypotensive effect was recorded the PRA was definitely lower during pindolol treatment

Summing up at least three mechanisms seem to be involved in the antihypertensive effect of pindolol namely 1) a negative chronotropic effect on the heart 2) a decrease in peripheral vascular resistance observed under certain conditions 3) an increase in vascular capacitance which effects the venous return This mechanism might explain why the lower heart rate was not compensated for by an *increase in stroke volume*

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Long-term Hypotensive Effect of Atenolol (ICI 66 082), a New β-adrenergic Blocking Agent

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ABSTRACT A report is given from an on going multicenter trial in Sweden in which 117 hypertensive patients have been treated with a new cardioselective β adrenergic blocking agent atenolol (ICI 66 082, Tenormin®) for an average of six months (range 2–21) Statistically significant reductions of BP were observed recumbent by 29/19 mmHg ($p<0\ 0001$) and standing by 28/18 mmHg ($p<0\ 0001$) Few and comparatively mild side-effects were seen

The β adrenergic blocking agent propranolol was first shown to have an antihypertensive effect a decade ago (13) This effect has been confirmed in later propranolol studies (6 10 12 14 15) and in reports on other β blockers (11)

With regard to propranolol it has been claimed that it reduces elevated BP as effectively as any other regimen in use today (15) and in the vast majority of patients propranolol is efficient and well tolerated This could explain its increasing use in the treatment of hypertension

The present report deals with early experience in hypertension with a new β blocker ICI 66 082 (atenolol) which in theory would seem to offer certain advantages over currently used β adrenergic antagonists

PHARMACOLOGY OF ATENOLOL

Atenolol (Tenormin®) is a selective β 1 receptor blocker or in other words cardioselective This compound has no sympathomimetic or partial agonist effect It also lacks local anesthetic properties (membrane stabilizing cardiodepressive or direct negative inotropic action) In animal autoradiography studies it has been shown not to cross the blood-brain barrier Its β-1-receptor blocking potency per mg is quite similar to that of propranolol as judged from its effect on isoprenaline induced tachycardia (1) The plasma half life of atenolol in man is approximately 6 hours

The structural formula of atenolol is illustrated in Fig 1 and a list of its pharmacological properties in comparison with those of some other β adrenergic blocking agents is given in Table I

MATERIAL AND METHODS

The study comprised 117 patients 111 with essential and 6 with secondary hypertension 71 men and 46 women with an average age of 50 years (range 30–73) Sixty two patients were previously untreated Applying the WHO criteria 78 patients were classified as having stage 1 hypertension 33 stage 2 and 6 stage 3 hypertension

The study was designed as an open out patient multi center trial BP after 5 min of recumbent rest and 2 min of standing was recorded using a mercury manometer with a cuff 13 cm wide The disappearance of the Korotkoff sounds (phase V) was taken as the diastolic BP

A starting dose of 50 mg b i d of atenolol was used and in most cases it was increased to 100 mg b i d following one week of treatment Occasionally a daily dose up to 800 mg was administered The average daily dosage was 211 mg (range 50–800) Atenolol was the only drug administered in 94 patients while 13 received combined therapy with hydralazine and 10 with diuretics The average duration of treatment was 6 months (range 2–21)

Initially patients were seen after two and four weeks of treatment during continued treatment at intervals up to three months At each revisit the patients were asked to report side-effects but a special check list was not used

A number of laboratory parameters were checked before and repeatedly during treatment These included Hb and serum creatinine concentration WBC and differential count S-GOT S-GPT alkaline phosphatase bilirubin concentration and uric acid in serum FBS and urinary excretion of albumin

Table I *Pharmacological properties of atenolol and some other β-adrenergic blocking agents*

	Blocks β	Blocks $β_2$	Sympatho-mimetic	Membrane stab l z ng	Penetrates blood–bra n barrier
Atenolol	+	–	–	–	–
Propranolol	+	+	–	+	+
Practolol	+		+	–	–
Oxprenolol	+	+	+	+	+
Alprenolol	+	+	+	+	+
Pindolol	+	+	+	+	+

RESULTS

The average reduction of recumbent BP and heart rate and of standing BP in all 117 patients was quite pronounced and statistically highly significant (Table II Figs 2 and 3) Similarly the therapy with atenolol as the sole antihypertensive agent in 94 patients caused statistically significant reductions of BP and heart rate (Table III)

As expected combined therapy with atenolol and hydralazine or with atenolol and a diuretic caused an even more pronounced reduction of BP (Tables IV and V)

The effect of atenolol in 62 previously untreated patients is illustrated in Table VI Out of these 62 patients 58 received atenolol as the sole therapy while four were treated with hydralazine or diuretics as well

Twenty four patients reported side effects which in seven patients motivated a withdrawal of treat t with atenolol (Table VII) One patient displayed a temporary small rise of S GOT Otherwise there were no significant changes in the laboratory parameters

In eight patients atenolol alone did not reduce BP at all An analysis of data from these patients failed to reveal any distinguishing features (age sex known duration of hypertension initial BP or heart rate WHO group dosage heart size or renal function) The lack of response in this group thus remains unexplained

DISCUSSION

When evaluating any new drug there is always a need for controlled comparisons e g with placebo as well as long term open studies preferably of a large number of patients in order to evaluat factors such as side effects long term toxicity and drug tolerance The present study can be regarded as the *first phase of such a long term on going follow up* study of atenolol in the treatment of hypertension

Today there is little doubt that β adrenergic blocking agents e g propranolol have a useful antihypertensive effect and in many clinics—including those participating in the present study—these agents have become the drugs of first choice *in the treatment of hypertension*

It could even be argued that there already is a

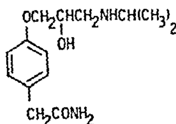


Fig 1 Structural formula of atenolol

Table II *Effect of atenolol in an average dose of 211 mg/d in the 117 patients (mean ±S E M)*

	Before	During	Difference
Recumbent			
Systol c BP	180+2 6	151+? 6	29
Diastol c BP	110+1 5	91+1 2	19
Heart rate	80+1 5	6?+1 1	18
Standing			
Systol c BP	175+2 7	147+2 4	28
Diastol c BP	114+1 6	96+1 1	18

S gnificance of the d fference $p<0.0001$

Table III *Effect of atenolol in an average dose of 192 mg/d used as the sole therapy in 94 patients (mean ±S E M)*

	Before	During	Difference
Recumbent			
Systolic BP	177±2 8	150±3 1	27
Diastolic BP	108±1 5	90±1 4	18
Heart rate	81±1 7	63±1 2	18
Standing			
Systolic BP	174±3 1	147±2 8	27
Diastolic BP	112±1 5	95±1 3	17

Significance of the difference $p<0\ 0001$

sufficient number of β adrenergic blocking agents available today as well as clinical data to support their use in the treatment of hypertension to make the introduction of a new agent seem superfluous However as atenolol from a theoretical point of view would seem to offer certain advantages over currently used β blockers we regarded it important to perform the present clinical evaluation

Thus the cardioselectivity of atenolol could be expected to reduce the risk of obstructive respiratory symptoms Moreover as vascular β 2 receptors are left unblocked by atenolol it seems probable that acute rises of BP e g due to stress induced release of circulating catecholamines would be less marked than during treatment with β 1 and β 2 receptor blocking agents The lack of a sympathomimetic effect of atenolol could be expected to be an advantage at least in the treatment of severe hypertension in analogy with what has been claimed for propranolol (9)

That atenolol does not readily penetrate the *blood–brain barrier has so far been shown only* in autoradiography studies in mice However since this inability to reach the CNS reflects the poor lipid solubility of atenolol a similar poor penetration of the blood–brain barrier could be expected in man If indeed atenolol does not reach the CNS—or does so only in minute amounts—this could be expected to reduce side effects such as vivid dreams hallucinations and depression occasion

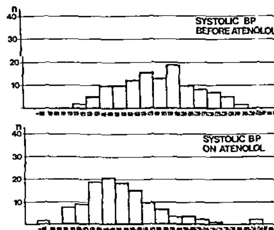


Fig 2 Systolic recumbent BP before and during treatment with atenolol

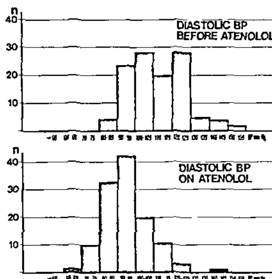


Fig 3 Diastolic recumbent BP before and during treatment with atenolol

Table IV *Effect of atenolol in an average dose of 292 mg/d in combination with hydralazine in an average dose of 146 mg/d in 13 patients (mean ±S E M)*

	Before	During	Difference
Recumbent			
Systolic BP	195±8 4	157±3 7	38
Diastolic BP	122+5 3	96±2 0	26
Heart rate	71±3 1	59±1 8	12
Standing			
Systolic BP	182±6 3	153±3 9	29
Diastolic BP	126+5 8	100±1 4	26

Significance of the difference $p<0\ 0001$

Table V *Effect of atenolol in an average dose of 294 mg/d in combination with diuretics in 10 patients (mean ±S E M)*

	Before	During	Difference
Recumbent			
Systolic BP	192±7 6	152±4 6	40
Diastolic BP	120±5 8	91±3 1	29
Heart rate	76±3 1	59±1 7	17
Standing			
Systolic BP	174±8 1	142±4 7	32
Diastolic BP	122±5 7	95±2 6	27

Significance of the difference $p<0\ 0001$

ally experienced with other β adrenergic blocking agents

Finally the lack of a membrane stabilizing effect is probably of little significance in most clinical applications as to elicit this effect even with e g propranolol considerably higher dosages are required than those usually applied (2) Only in cases of accidental over dosing could the lack of a membrane stabilizing effect conceivably be an advantage by reducing the risk of myocardial depression

The present study—which is intended to continue for quite some time for reasons already mentioned—demonstrated significant reductions of BP This is in agreement with our initial observations in smaller numbers of patients treated in ital (8) and as out patients (5) The reduction BP is of at least the same order as that which we have previously reported with propranolol (6) As with propranolol the addition of hydralazine (7) proved to be more efficient than the use of the β blocker alone Furthermore the combined treatment with atenolol and diuretics seemed to be more effective than treatment with atenolol alone From the results of the present study it could be expected that atenolol has an antihypertensive effect of at least the same order as propranolol Obviously a controlled study will be needed before such a claim can be substantiated

Table VI *Effect of atenolol in an average dose of 203 mg/d in 62 previously untreated patients (mean ±S E M)*

	Before	During	Difference
Recumbent			
Systolic BP	186±3 2	156±4 0	30
Diastolic BP	110±1 7	92±1 7	18
Heart rate	83±1 8	62±1 5	21
Standing			
Systolic BP	182±3 4	153±3 2	29
Diastolic BP	115±1 7	97±1 6	18

Significance of the difference $p<0\ 0001$

Table VII *Side effects during treatment with atenolol*

	No of pats	Comments
Fatigue	6	Atenolol withdrawn in one patient
Cold hands/ feet	4	
Seborrhea/ eczema	4	Atenolol withdrawn in one patient Symptoms disappeared completely in one patient following penicillin therapy Two patients without symptoms on continued atenolol therapy plus local treatment of the skin lesions
Depression mild	2	In one patient only when dosage was increased
Raynaud s phenomenon	1	Atenolol withdrawn Previously same effect with propranolol
Sinus bradycardia	1	Atenolol withdrawn
Vertigo	1	
Insomnia	2	
Sweating	1	
Headaches	1	Atenolol withdrawn
Temporary rise of S GOT	1	72 U/l recorded (normal <30 U/l) Initial abnormality in liver function tests
Dyspnea	1	Atenolol withdrawn
Dryness of eyes	1	No symptoms when dosage was reduced from 200 to 150 mg/d Previously allergic toxic reactions to sulphonamides bethanidine nitrofurantoin and propranolol

With regard to side effects it can be noted that fatigue was the most common complaint in a few instances experienced as muscle fatigue e g when climbing stairs The underlying mechanism of this phenomenon—which is seen with other β blockers as well—is not fully known Most likely it is due to reduced blood flow secondary to the reduction of cardiac output This could also explain the complaints of cold extremities Another possibility is that because vascular β 2 receptors are left unblocked there may be some vasodilatation during increased release of catecholamines as during physical exercise This could in turn cause a less

pronounced rise of BP—as compared to the un blocked or β 1 and β 2 receptor blocked situation —thereby causing fatigue of the working muscle group

Skin lesions occurred in 4 patients in this long term study In view of the recent reports on skin lesions during treatment with practolol and oxprenolol (3) extra care was taken to evaluate these changes In one patient—a man aged 47—all symptoms disappeared following penicillin therapy He is still taking atenolol and has no skin symptoms Two more patients are symptomless on atenolol after local treatment of the skin lesions In the fourth patient atenolol was withdrawn In none of the patients were the skin lesions of the kind described during practolol treatment (4) and skin biopsy with immunofluorescence microscopy has revealed only mild unspecific inflammation

All patients have been actively asked about possible eye symptoms and concerning the patient—a woman aged 55—complaining of dry eyes it should be noted that she has previously reacted with toxic allergic skin reactions and a possible drug induced SLE state following treatment with sulphonamides bethanidine nitrofurantoin and propranolol Examination by an ophthalmologist revealed no signs of keratoconjunctivitis sicca and no evidence of any conjunctival or corneal changes which could be attributed to her treatment with atenolol

It therefore seems that the skin and eye symptoms observed in the present long term study are most likely unrelated to the treatment However as with all new drugs continued careful observation in these areas is essential

In conclusion we feel that atenolol has a useful antihypertensive effect while at the same time showing few and relatively mild side effects It would appear that atenolol (Tenormin®) is at least comparable in its antihypertensive potency to currently used β adrenergic blocking agents while at the same time offering certain clear advantages e g by being cardioselective and not penetrating into the CNS

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Hemodynamic Long-term Effects of Timolol at Rest and during Exercise in Essential Hypertension

Per Lund Johansen

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ABSTRACT Sixteen men with previously untreated essential hypertension in WHO stage I have been studied as out patients Oxygen consumption, heart rate (HR), cardiac output (Q̇) (Cardiogreen) and intraarterial brachial pressure were recorded at rest in supine and sitting position and during steady state work at 300, 600 and 900 kpm/min The subjects were treated with timolol as the sole drug for one year and the hemodynamic study was repeated BP was reduced approximately 18% at rest and 14% during exercise, HR approximately 26% and the cardiac index 28% at rest supine and 32% at rest sitting During exercise the reductions in Q̇ were 25–30% The calculated total peripheral resistance was significantly increased at rest as well as during exercise The product of mean arterial pressure and HR was reduced about 40% No severe side-effects were seen

Timolol is a relatively new non cardioselective β blocker without intrinsic sympathomimetic activity (13) Clinical cross-over trials in hypertensive subjects have demonstrated that it reduces BP similarly to alprenolol oxprenolol and propranolol (10) The fall in BP during short term use (less than one week) of β blockers is typically associated with reduction of cardiac output (Q̇) and rise in total peripheral resistance (TPR) above pretreatment values (4 5 11 12 14) Several studies have shown that Q̇ remains low after long term use of propranolol (3 4 12) and alprenolol (8) although TPR seems to decrease gradually in some patients (4 12) A preliminary report on a small group of patients studied at rest supine indicated no fall in Q̇ after long term use of timolol in contrast to propranolol and the BP reduction was due to a drop in TPR (2) Therefore timolol would seem to be of particular interest in hypertension

The present work is a study of the central hemodynamics at rest and during exercise in a relatively homogeneous group of patients with essential hypertension studied before and after one year on timolol therapy

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MATERIAL

The study includes 16 men aged 32–56 years (mean 47 4) with untreated essential hypertension in WHO stage I Secondary hypertension was excluded by the usual routine procedures (6) All were without symptoms the hypertension being discovered at routine controls by a health officer or general practitioner and established by at least three visits to the Out patient Clinic at Medical Department A Haukeland Hospital The mean and S D for body weight and BSA before treatment were 79 8±8 5 kg and 1 97±0 11 m² After one year on therapy there were no significant changes in body weight

METHODS

The subjects were studied hemodynamically during strictly standardized conditions at rest supine and sitting and during bicycling in steady state at 300 600 and 900 kpm/min Oxygen consumption (VO_2) intraarterial pressure (brachial artery) heart rate (HR) and Q̇ (Cardiogreen) were measured in duplicate in each situation The methods have been described previously in detail (6 7) The subjects were informed about the nature and purpose of the study and consent was obtained from all

All studies were made on an out patient basis After a treatment period of 11–12 months the hemodynamic study was repeated The difference between the hemodynamic results at the first and the second study was tested by Student s *t* test

The present study does not include any untreated control group However previous work (7) has shown that in similar untreated subjects the hemodynamic parameters at re study after one year do not differ significantly from the first

Table I *Oxygen consumption (VO₂) cardiac index (CI) stroke index (SI) and heart rate (HR) before (I) and during (II) therapy mean difference (II–I) and p value of paired sample test*

	Rest				Work (kpm/min)					
	Supine		Sitting		300		600		900	
	I	II	I	II	I	II	I	II	I	II
VO_2 (ml/min/m²)										
Mean			144 9	151 1	546 5	568 7	735 3	834 6	1 154 5	1 269 9
S D			13 9	17 9	78 7	57 6	69 5	89 4	115 4	142 7
II–I			+6 2		+22 2		+99 3		+115 4	
p			n s		n s		<0 01		<0 05	
CI (l/min/m²)										
Mean	3 70	2 68	3 10	2 11	6 53	4 33	7 56	5 65	9 08	6 73
S D	*0 52*	*0 29*	*0 47*	*0 20*	*1 15*	*0 43*	*0 82*	*0 55*	*1 03*	*1 36*
II–I	−1 02		−0 99		−2 10		−1 91		−2 35	
p	<0 001		<0 001		<0 001		<0 001		<0 001	
SI (ml/stroke/m²)										
Mean	52 3	51 2	41 3	39 3	59 1	54 8	56 3	57 4	56 5	56 7
S D	5 8	6 1	5 4	4 2	6 9	6 0	7 0	5 2	6 0	10 8
II–I	−1 1		−2 0		−4 3		+1 1		+0 2	
p	n s		n s		<0 01		n s		n s	
HR (beats/min)										
Mean	70 9	52 6	75 1	53 9	110 3	81 2	134 4	97 6	161 3	118 6
S D	8 7	4 7	9 3	4 9	12 5	6 9	13 1	7 5	16 5	8 0
II–I	−18 3		−21 2		−29 1		−36 8		−42 7	
p	<0 001		<0 001		<0 001		<0 001		<0 001	

Treatment

The patients received timolol as tablets 5 mg b d s (at 7 00 a m and 5 00 p m) In 10 patients the dose was increased to 10 mg b d s within 4 months and in one patient to 15 mg b d s No other drugs or any diet restrictions were given On the day of the second hemodynamic dy the patients took their morning dose at 7 00 a m hemodynamic study was performed between 9 00 and 00 a m

Side effects

No subjects had to be withdrawn from the study During the first 2–3 weeks 3 patients experienced pronounced fatigue in thighs and legs when climbing stairs One subject felt very dizzy during the first few days and the dose had to be temporarily reduced At the end of the study these complaints had disappeared completely One subject complained of cold feet this condition lasting throughout the study All subjects were actively employed and in relatively good physical condition during the study

RESULTS

Casual blood pressure and heart rate

The casual BP (sitting) dropped in all subjects the mean value from 171/114 mmHg before the start to 142/97 mmHg at the last control shortly before the second hemodynamic study The casual diastolic pressure (DAP) was reduced 10 mmHg or more in all but 3 subjects These three had reductions in systolic arterial pressure (SAP) of 30 15 and 30 mmHg The mean HR dropped from 89 to 58 beats/min

Hemodynamic data

The hemodynamic data are shown in Tables I and II and Fig 1

Oxygen consumption

VO_2 did not change significantly at rest or during the 300 kpm/min work load At the two highest work levels VO_2 increased significantly by 14 and 10% respectively

Cardiac index (CI)

CI decreased in all subjects at rest supine and sitting at all three work levels The mean decrease at rest was about 1 0 l/min/m² both supine and sitting or 28 and 32% respectively the changes being highly significant At rest sitting the reduction was ≥12% in all subjects the greatest reduction being 48% All subjects had values below 2 5 l/min/m² after therapy none before During exercise the absolute

Table II *Systolic (SAP) diastolic (DAP) and mean arterial pressures (MAP) total peripheral resistance index (TPRI) before (I) and during (II) therapy mean difference (II–I) and p value of paired sample test*

	Rest				Work (kpm/min)					
	Supine		Sitting		300		600		900	
	I	II	I	II	I	II	I	II	I	II
SAP (mmHg)										
Mean	151 6	128 8	167 4	141 8	190 1	162 1	193 2	166 3	213 9	187 7
S D	9 1	18 5	10 5	18 6	16 1	21 8	12 4	19 3	16 8	20 6
II–I	−22 8		−25 6		−28 0		−26 9		−26 2	
p	<0 001		<0 001		<0 001		<0 001		<0 001	
DAP (mmHg)										
Mean	88 9	72 7	99 8	82 9	104 0	88 4	103 1	88 4	112 1	97 7
S D	6 1	9 3	8 2	7 9	9 8	10 5	6 1	9 2	8 2	7 3
II–I	−16 2		−16 9		−15 6		−14 7		−14 4	
p	<0 001		<0 001		<0 001		<0 001		<0 001	
MAP (mmHg)										
Mean	113 1	92 8	127 1	105 2	140 9	119 6	140 1	120 2	154 0	136 9
S D	6 2	11 8	9 8	10 6	12 5	18 1	7 5	12 7	11 0	13 8
II–I	−20 3		−21 9		−21 3		−19 9		−17 1	
p	<0 001		<0 001		<0 001		<0 001		<0 001	
TPRI (dyn/sec cm⁻⁵m²)										
Mean	2 489	2 801	3 368	4 073	1 760	2 173	1 495	1 723	1 377	1 726
S D	349	480	512	604	240	343	160	296	210	553
II–I	+312		+705		+413		+228		+349	
p	<0 05		<0 01		<0 01		<0 01		<0 01	

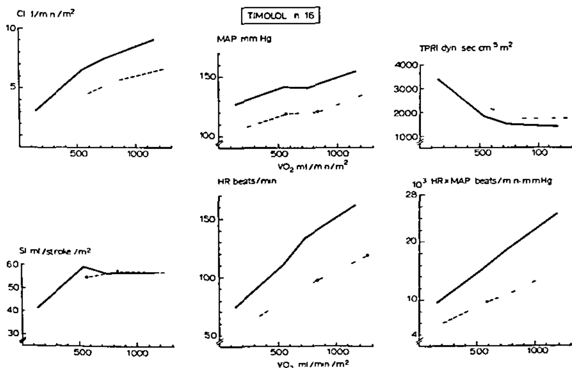


Fig 1 Hemodynamic changes at rest sitting and during exercise before (—) and after ( ) treatment with timolol Mean values Abbreviations as in Tables I and II

reductions of CI were greater than at rest about 2 l/min/m at the three work levels or 32 25 and 26% Thus Q during work was approximately 4 l/min lower after therapy than before

Arteriovenous oxygen difference (A–V)O

As posttreatment VO was unchanged or increased there was a marked increase in (A–V)O The calculated (A–V)O increased from 46 8 to 71 6 ml/l at rest from 83 7 to 128 4 ml/l at the 300 kpm load from 97 3 to 147 7 at the 600 kpm load and from 127 2 to 188 7 ml/l at the 900 kpm load

Heart rate

HR decreased 10% or more in all subjects at rest and during all three work levels At rest supine and sitting the mean HR decreased 18 and 21 beats/min (26 and 28% respectively) At rest supine 4 patients had a HR ≤48 beats/min after therapy During exercise the reductions of HR were 29 37 and 43 beats/min or 26 27 and 26% at the three work levels.

Stroke index (SI)

At rest supine and sitting there were no significant changes in SI During exercise SI was significantly lower after therapy at the 300 kpm/min load at the two highest work levels the mean SI was almost

Arterial pressure

Although the casual BP had decreased in all one subject demonstrated no decrease in mean arterial pressure (MAP) at rest sitting and during the 300 kpm/min load and only a modest reduction at the other two work levels when studied hemodynamically This patient had a poor response to timolol After the hemodynamic study he received 2 mg polythiazide every second day in addition to 15 mg b d s of timolol The casual BP dropped from 170/110 to 135/95 mmHg Table II shows that the absolute decreases in SAP were greater than the decreases in MAP the decreases in DAP somewhat less The relative changes were rather similar Before therapy 14 patients had DAP>90 mmHg at rest sitting after therapy only 3 (96 91 and 91 mmHg) In the remaining 15 patients the MAP had dropped at rest as well as during exercise At rest sitting the reductions of MAP were 10% or more in 14 patients (9% in one) the mean decrease being 18% at rest supine and 17% at rest sitting During exercise the mean decreases were 15 14 and 11% respectively at the three work levels

Total peripheral resistance

Before therapy TPR index (TPRI) at rest sitting and during exercise was higher in all subjects than in normotensive controls of similar age (6) Compared with the pretreatment value TPRI rose significantly both at rest supine and sitting (13% and 21%) and at the three work levels (23% 15% and 24%) At rest sitting TPRI rose in all but one subject the rise being 10% or more in 11 During exercise TPRI rose in all but one subject At the 300 kpm load the rise was 10% or more in 13 A 10% decrease in TPRI at rest sitting and during two work loads was not seen in any subject

DISCUSSION

From a clinical point of view timolol induced a satisfactory reduction of BP in all but one subject (who responded well later when a diuretic was added to the timolol therapy) The dose regime was simple and apart from muscular fatigue in three subjects and dizziness in one during the first weeks no severe side-effects were seen though one subject complained of cold feet during the entire study The changes in central hemodynamics were very consistent the main ones being marked reductions of HR and CI TPRI was higher than before therapy

Thus this study does not confirm the preliminary results of Franciosa et al (2) suggesting no decrease in Q and a decrease in TPRI during long term therapy with timolol in contrast to propranolol The reason for this discrepancy is not clear In the relatively small group of patients examined in their study the reductions of BP and HR were very slight and this might partly explain why the Q did not decrease during their 5 week trial Their patients were studied only at rest supine our patients were studied during five different situations all with the same type of changes

The major hemodynamic changes resemble those seen after long term use of alprenolol (8) atenolol (1 9) and propranolol (3 4 12) The pressure

reductions induced by alprenolol were smaller—*this could be due to the dose or to the intrinsic* sympathomimetic effect of alprenolol The pressure reductions obtained by atenolol in an equivalent group of patients (9) were very similar at rest as well as during exercise With atenolol the TPRI changes at rest supine and during 600 and 900 kpm/min work load were small and insignificant in contrast to timolol on which treatment TPRI increased *significantly in all* situations

Some difference also seems to exist with respect to the stroke volume The posttreatment SI during exercise was significantly higher at the two highest work levels with alprenolol and atenolol thus partly compensating for the reduction of HR (8 9) No such increase was seen with timolol

The product of MAP and HR was markedly decreased about *40%* at rest and *37%* during exercise This change should lead to a substantial reduction of the myocardial oxygen requirement

Timolol induced the lowest Q during exercise a reduction of about 4 l/min This was compensated by a marked increase in $(A-V)O_2$ which rose to 189 ml/l 40% more than in normotensive controls (6) Apart from temporary muscular fatigue this marked change in the circulatory system did not induce subjective side effects in this type of patient None of the subjects found the 900 kpm/min load more strenuous after one year of therapy than before treatment started All the subjects were physically active several enjoying rather vigorous physical exercise like running in the mountains and cross-country skiing

It is indeed puzzling how well a β-blocker like timolol is tolerated even though it induces a rather abnormal hemodynamic situation The long term effects of these changes are not known and it should be stressed that the patients in this study had an almost normal heart pump before therapy started Whether patients with a subnormal cardiac output at rest and during exercise will tolerate a similar reduction *of cardiac output is less certain*

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A Blood Pressure Information Campaign Including Mass Screening for Hypertension in Copenhagen Supermarkets

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ABSTRACT During its "Heart week in Feb 1975 the Danish Heart Foundation drew the attention of the public to the importance of blood pressure measurements as a vital part of health control and prevention In all 24 thousand men and women attending supermarkets in Copenhagen took advantage of an offer to have their BP checked 23% of the screened who had systolic BP ≥age+110 (and this sum exceeded 145) and/or diastolic BP ≥100 mmHg for all ages were advised to contact a general practitioner for further evaluation The campaign showed that it is possible to measure BP and obtain reliable results in an easy, quick inexpensive and unorthodox way accepted by a public accustomed to free medical care

Elevated blood pressure casual or basal labile or fixed systolic or diastolic at any age in either sex emerges as the single most potent contributor to cardiovascular morbidity and mortality (11)

It has been demonstrated that antihypertensive treatment has lowered the morbidity and mortality of cardiovascular complications (8 17 18 21) The major problems in controlling hypertension—an extremely common condition which often goes undetected untreated or inadequately treated (1 5 6 7 9 14 15 16 19 20)—are getting the hypertensives to medical care and motivating them for lifelong follow-up and probably lifelong treatment To meet this challenge a community screening and information program is necessary not only to detect the hypertensives but first of all to stress the importance of regular BP measurements

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The purpose of this communication is to present a BP community information program including screening for hypertension in Copenhagen during one week

MATERIAL AND METHODS

The Danish Heart Foundation held its annual Heart week in Feb 1975 The theme this year was arterial blood pressure An easy to-read pamphlet with illustrations was printed in 300 000 copies and distributed mainly through supermarkets schools physicians and members of the Foundation Besides using posters and advertisements the Foundation organized BP measurements in several cities in Denmark In Copenhagen 13 supermarkets were contacted all of which showed great interest in helping with this screening and information program The largest supermarket had approximately 125 000 customers a week the smallest 10 000–15 000 The Foundation had decided that 2 D cr (50 35) should be paid by each person measured For this price they would also receive the BP pamphlet In only two of the supermarkets did the customers in fact pay for themselves since in the rest the owners offered to make the contributions

The measurements were made by approximately 90 persons—medical students nurses and laboratory technicians Almost all had some experience in measuring BP but they were of course further instructed to insure that the measurements were made in the same way in either arm with the subject just seated after standing in a line for 2–10 min The cuff was placed over the bulge in the upper arm which was stretched out but relaxed and supported on a table and then rapidly inflated to 200 mmHg and deflated at a rate of 2–3 mm/sec Systolic BP was determined by the first perception of sound and diastolic at the point at which the sounds became muffled (phase 4) If the systolic sound was audible immediately after inflation the cuff pressure was allowed to fall to zero and a fresh inflation to 250 mmHg was performed Readings were made to the nearest 2 mm

The screening was performed on five consecutive workdays on the first four at 3 30–5 30 p m and on the fifth at 4 00–8 00 p m Every person measured received in

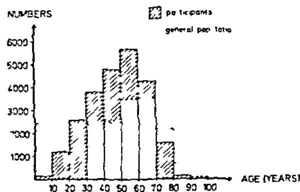


Fig 1 Age distribution of the participants and of a similar number distributed as the general population in the City of Copenhagen

addition to the BP pamphlet a card with the BP values If the systolic BP exceeded the persons age + 110 (and if this sum exceeded 145) and/or the diastolic BP exceeded 100 mmHg for all ages they were advised to contact a general practitioner for further evaluation

RESULTS

The public showed great interest in this screening Some of the supermarkets registered almost twice as many customers during the screening hours compared with the same hours in other weeks In all 24 377 persons (13 747 women and 10 630 men) were checked The age distribution is presented in Fig 1 (6% ≤19 26% = 20–39 43% = 40–59 and 25% ≥60 years of age) The total percentage of women and men corresponded well to the total sex distribution in Copenhagen

Each member of the screening staff carried out an average of 22 measurements per hour Depending on the supermarket this figure varied from 18 to 30

The cost for this screening expressed in US$ and including salary to the students ($7 per hour) transportation pamphlets cards and other materials was *$12 000 or 0 49 per measurement The income* totalled $7 700 So the expense for the Danish Heart Foundation was $4 300 or approximately 0 18 per measurement Of this amount $0 11 were for the BP pamphlet

Attendance was approximately the same in the supermarkets where people had to pay for themselves compared with those where the supermarket paid At a rough estimate during the screening hours 75% of the customers in the smaller supermarkets and 10% in the largest supermarket had their BP checked

Table 1 *Percentage of persons with systolic BP ≥160 mmHg and of persons with diastolic BP ≥100 mmHg (right arm)*

	Systolic ≥160		Diastolic ≥100 (phase 4)	
Age group	Women	Men	Women	Men
10–19	1	6	2	3
20–29	4	9	5	8
30–39	7	10	8	15
40–49	15	16	13	22
50–59	33	31	21	26
60–69	57	52	28	30
70–79	73	71	29	30
80–89	81	63	33	31

Altogether 5653 (23 1%) of the persons measured were referred to general practitioners for further evaluation 3 7% had systolic values ≥200 1 1% ≥220 and 0 2% ≥240 mmHg 7 3% had diastolic values ≥110 2 2% ≥120 and 0 7% ≥130 mmHg

Table 1 shows the percentage of persons with systolic values ≥160 mmHg and of persons with diastolic values ≥100 mmHg With increasing age a steadily increasing proportion of persons have systolic values ≥160 mmHg At the age of 60 more than half were found to have these values The diastolic pressure also rose with age but mostly before 50 years

Fig 2 shows median values for systolic and diastolic BP for men and women measured in the

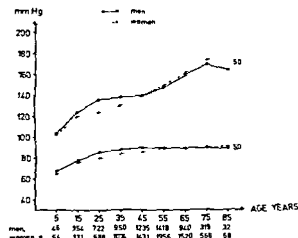


Fig 2 Systolic and diastolic BPs (right arm) in 13 704 men and women (median values)

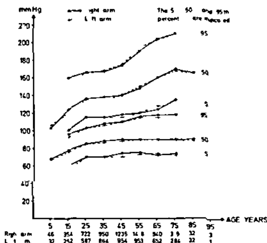


Fig 3 Systolic and diastolic BP in 10 630 men

right arm The systolic pressure increases almost linearly with age being higher in men than in women until the forties after which age the relation becomes reverse The diastolic pressure increases until middle age—being higher in men than in women until the fifties after which age the women equal the men—and then remains constant

Figs 3 and 4 show the 5th 50th and 95th percentiles for the BP by age for men and women The dispersion of the blood pressure especially the systolic values increases with age No systematic differences were found between values from right and left arms

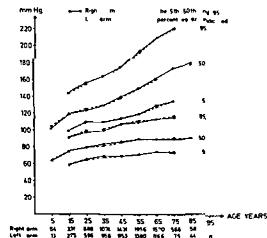


Fig 4 Systolic and diastolic BP in 13 747 women

DISCUSSION

The Danish health care system is organized so that nearly all inhabitants are able to get care without direct charges although most of them pay indirectly through taxes The system aims to provide treatment for disease and to a much smaller degree to prevent or postpone disease Approximately 98 5% of the total expenditure goes to treatment and less than 1 5% to prevention

Under the presumption that hypertension represents one of the greatest challenges in modern medicine and that organ damage should be prevented rather than treated the Danish Heart Foundation undertook a blood pressure campaign with the main purposes of informing the public about the hazards of elevated BP and underlining the importance of having BP measured regularly A further benefit would be to increase the physician s interest in the follow up and treatment of hypertension Furthermore the Foundation wanted to investigate whether BP measurements could be performed easily quickly and at low cost

In the afternoon hours of five consecutive days it was possible to screen more than 24 thousand men and women in 13 supermarkets in Copenhagen This great interest in BP measurements performed in a new way in Scandinavia showed that the public accepts investigations by non physicians—at least when they know that an accepted (although private) authority supports the program

The total percentages of women and men screened corresponded well to the total sex distribution in Copenhagen in contrast to the distribution of patients in general practice where women are overrepresented Several women mentioned that they could not drag their husbands to the doctor but that the men were willing to visit the *supermarket and have their BP checked there* The sample measured was underrepresented in the age groups below 30 and above 70 overrepresented in the rest

Of the persons measured 23% were referred to their own physicians for a follow up Our referral limits were somewhat higher than the WHO criteria for hypertension (≥160 and/or ≥95 mmHg) because we wanted the proportion of persons found normotensive by their physicians to be within acceptable limits

Our results based on screening in supermarkets were in agreement as far as the systolic values are concerned with other Scandinavian studies from

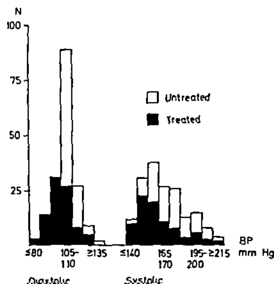


Fig 1 Distribution of supine systolic and diastolic BP in untreated (n=87) and treated (n=87) hypertensives at the screening examination

Uppsala The participants were invited by letter and asked to fast and refrain from smoking since the preceding midnight The examination started at 7 30 a m

BP measurements

The BP and pulse rate were measured after 10 min rest in recumbency The BP was recorded with a mercury manometer (Kifa Ercameter wall model) using a rubber cuff 12 5 cm wide and 35 cm long The measurements were performed on the right arm Systolic BP (SBP) and DBP were read to the nearest 5 mmHg The DBP was d when the sound had disappeared entirely ff phase 5)

stionnaire

Information regarding family history smoking habits physical activity and stress experience was collected by a self administered questionnaire presented elsewhere (9) The coding of marital status and social group classification—according to the three conventional groups—were based on interview reports

Anthropometric measurements

The relative body weight was calculated from actual over ideal weight obtained from the tables of Lindeberg et al (13) Subscapular skinfold thickness was measured with Harpenden s caliper

Laboratory investigations

The laboratory analyses of serum lipids serum uric acid serum creatinine and haematocrit were performed by the methods used routinely at the Department of Clinical Chemistry University Hospital An i v glucose tolerance test was performed by a method described previously on a randomly selected subsample (9)

Serum insulin was determined in duplicate using the Phadebas Insulin Test (Pharmacia Uppsala Sweden) This method is based upon the radioimmunosorbent technique described by Wide et al (19) The early serum insulin response to i v glucose was expressed as the mean value of the insulin concentrations determined at 4 6 and 8 min after the start of the glucose injection The late insulin response was expressed as the value at 60 min The serum insulin index was defined as the ratio between early insulin response and basal insulin concentration (20)

Electrocardiogram

A 12 lead ECG was recorded and evaluated according to the Minnesota code Possible LVH was defined as QRS axis deviation (code II 1) in combination with high QRS voltage (code III 1) Probable LVH was defined as any of these criteria in combination with ST–T changes (code III 1–3 and IV 1–3) Typical LVH was considered to be present when all three criteria were fulfilled

Statistical calculations

Conventional methods were used for calculating means and S D Significance of differences between mean values was estimated with Student s t test (2 tailed test) Logarithm transformed values were used when testing the means of serum insulin concentrations K values and serum triglycerides because these parameters were skewed to the right (9) The χ^2 test (with Yate s correction) was used for comparison of frequencies The accepted level of significance was $p<0\ 05$

RESULTS

According to the death certificates 86 of the men born in 1920–24 had died during the 10 years prior to the investigation However none had died from cerebral haemorrhage From the records of the Department of Medicine University Hospital (the only hospital in the City of Uppsala with emergency service) it was found that only 4 men had suffered a cerebrovascular lesion with long term sequelae during the same period Three men all hypertensives had suffered this cerebral accident after the age of 45

Prevalence and treatment of hypertension in the population

The questionnaire responses showed that 13 5% of the men had at some time been told that they had high BP At the examination 174 men were considered to be hypertensive a prevalence of 7 5% Eighty seven men were on treatment and in 48 of them (55 2%) this was adequate with a supine DBP below 105 mmHg Thus 27 6% of the total hypertensive population had satisfactory treatment The distribution of SBPs and DBPs in the treated and untreated groups is shown in Fig 1

Table I *Antihypertensive medication at screening in 87 men with hypertension*

	n	%
Diuretics	53	60 9
Beta blocking agents	33	37 9
Sympathicolytics	17	19 5
Hydralazine	16	18 4
Alpha methyldopa	6	6 9
Other	5	5 7
Unknown	3	3 4

The antihypertensive medication at the time of screening is shown in Table I Diuretics were used as the only drug by 19 5% and β blocking agents by 16 1% Thirty four men (39 1%) used various combinations in which diuretics featured in 92 1%

Family history of hypertension and cardiovascular deaths

A history of dead parents was obtained more often in the hypertensives than in the population sample (Table II) Death due to myocardial infarction and cerebrovascular lesion was also more common among the parents of the hypertensives However the only difference that reached a significant level was found in fathers of treated hypertensives dead in myocardial infarction A history of hypertension was obtained significantly more often among the parents and siblings of the hypertensives than in the population sample

Marital status and social class

There were no differences in marital status between the hypertensives and the total population or between treated and untreated hypertensives The distribution by social group showed an over representation of group 2 in the hypertensive population the difference being significant ($p<0.05$) for untreated hypertensives compared with the total population

Smoking habits (Table III)

The frequency of smokers was approximately 10% lower in the hypertensives than in the total population ($\chi^2=3.16$ $p<0.10$ for treated hypertensives) Among the treated hypertensives there were more men who had never smoked than among the total population The percentages of ex smokers were the same in the different groups No significant differences were found with regard to the frequency of cigarette smokers

Table II *Frequency (%) of dead parents and deaths due to myocardial infarction (MI) and cerebrovascular lesion (CVL) and family history of hypertension among untreated and treated hypertensives compared with the population sample*

	Hypertensives		Population sample
	Untreated	Treated	
Father dead	73 6	82 8*	70 3
Mother dead	66 7*	58 6	52 9
Father dead MI	17 2	19 5	11 9
Father dead CVL	13 8	14 9	8 9
Mother dead MI	9 2	5 7	6 2
Mother dead CVL	13 8	13 8	8 5
Father hypertension	20 7	17 2	10 9
Mother hypertension	35 6*	50 6	24 2
Brother hypertension	6 9	11 5* *	3 4
Sister hypertension	8 0*	16 1 *	3 3

* $p<0.05$ ** $p<0.01$ * * $p<0.001$ compared with the population sample

Physical activity and stress experience

The degree of physical activity was evaluated at work and during leisure There were no differences in physical activity at work Thus 36% of the untreated and 39% of the treated hypertensives had predominantly sedentary work The corresponding percentage was 35% in the total population Heavy manual work was reported by 14% in both untreated and treated hypertensives compared with 16% in the population studied Physical activity during leisure was similar in all groups

A history of constant stress during the last 5 years was reported by 5% of the hypertensives which was identical to the rate in the total population A

Table III *Smoking habits in men (%) with untreated and treated hypertension and in the total population*

	Never smoked	Ex smokers	Smokers
Untreated hypertensives	29 9	27 6	42 5
Treated hypertensives	36 0	23 3	40 7
Total population	25 8	23 2	51 0

* Refrained from smoking for more than one month
* $p<0.05$ compared with total population

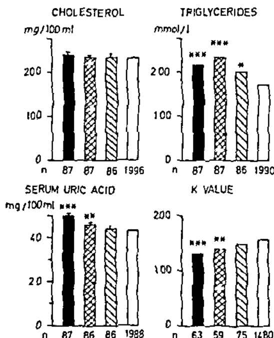


Fig 2 Serum lipids serum uric acid and i v glucose tolerance (K value) in middle aged men with treated (■) and untreated (■) hypertension and in weight matched controls (▨) of the untreated hypertensives compared with controls from a population sample of the same age (□) (* $p<0.05$ ** $p<0.01$ *** $p<0.001$ compared with the population sample)

history of constant stress during the last year was obtained in 8% of the untreated and in 13% of the treated hypertensives compared with 8% in the total population A history of occasional periods stress experience during the last 5 years was by 40% and 46% of untreated and treated hypertensives respectively This frequency was 39% in the total population None of these differences were significant

Clinical data

The untreated hypertensives had significantly higher BPs than the treated (Table IV) The pulse rate was significantly higher in the untreated hypertensives than in the population sample as well as in the treated hypertensives The lower pulse rate in the latter group may reflect the use of β blocking agents

The hypertensives untreated as well as treated were more obese as shown by the higher relative body weight and the greater skinfold thickness A history of weight gain of >10 kg after the age of 30 was significantly more common among the hypertensives ($p<0.001$) This was reported in 52 9% of untreated and in 56 3% of treated hypertensives and in 30 5% of the total population

The questionnaire responses revealed that untreated hypertensives reported cholecystectomy and a history of renal stones more frequently than the total population ($p<0.001$)

Serum lipids

The mean values of serum lipids are shown in Fig 2 The serum triglyceride (TG) values were significantly higher in the hypertensive untreated as well as treated compared with the population sample On the other hand in the weight matched controls the TG concentration was lower but not significantly than in the untreated hypertensives The serum cholesterol values were similar in all four groups

The prevalence of hyperlipidaemia was 47 1% in untreated hypertensives when using a limit of the 80th percentile of the serum lipid values in the total population (265 mg/100 ml for cholesterol and 2 27 mmol/l for TG) The corresponding percentage in the weight matched control group was 36 0%

Table IV *Some clinical parameters in hypertensives and in the population sample*

	Hypertensives					
	Treated (n=87)		Untreated (n=87)		Population sample	
	(Mean)	(S D)	(Mean)	(S D)	(Mean)	(S D)
Systolic BP (mmHg)	163 5	21 8	173 7**	18 4	131 5	16 5
Diastolic BP (mmHg)	101 8	11 8	111 1***	7 4	82 7	10 2
Pulse rate (beats/min)	70 1	12 7	76 7***	12 6	68 4	10 4
Weight index	1 17	0 16	1 20***	0 19	1 09	0 13
Subscapular skinfold* (mm)	20 0	5 7	21 4***	6 4	16 5	6 0

* Untreated hypertensives (n=46)
*** $p<0.001$ compared with the population sample

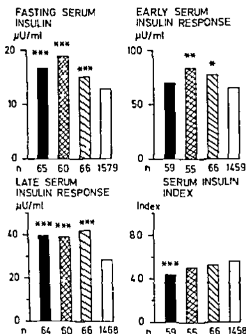


Fig 3 Results of serum insulin determinations in the same four groups as in Fig 2 Symbols and statistical analyses as in Fig 2

(p>0 05) and 33 2% in the total population (p<0 01) Isolated hypertriglyceridaemia occurred in 28 7% of the untreated hypertensives compared with 16 3% of the controls (p=0 05)

Serum uric acid

Serum uric acid (SUA) concentration was significantly higher in the treated hypertensives than in the population sample (Fig 2) The mean values were 5 05±1 08 and 4 30±0 93 mg/100 ml respectively The untreated subjects had a mean value of 4 64±1 10 mg/100 ml significantly lower than in the treated group (p<0 01) but significantly higher than in the population sample This elevation could not be explained by obesity alone since SUA in the untreated hypertensives with weight index ≤1 10 (n=33) did not differ from those with weight index >1 10 the values being 4 55±1 02 and 4 70±1 16 mg/100 ml respectively The former value was significantly higher (p<0 01) than that of the corresponding control group 3 91±0 73 mg/100 ml but there was no difference between the untreated hypertensives with weight index >1 10 and their matched controls whose mean was 4 72±0 91 mg/100 ml

Glucose tolerance

Significantly lower K values were found for i v glucose tolerance in untreated and treated hypertensives than in the population sample (Fig 2) Mean values were 1 38 1 30 and 1 56 respectively The mean K value of the weight matched control group was 1 48 which did not differ significantly from that of the untreated hypertensives and the population sample

The prevalence of low K values in the four groups is shown in Table V The frequency in the hypertensive groups was higher than in the population sample However the frequency of K values <1 10 in the weight matched controls did not differ significantly from that in the hypertensive groups

Serum insulin

The results of the serum insulin determinations are summarized in Fig 3 The mean values of fasting serum insulin concentrations and early and late serum insulin responses to i v glucose were significantly higher in the hypertensives untreated as well as treated than in the population sample The mean fasting serum insulin concentration was 19 0 μU/ml in the untreated hypertensive group compared with 16 1 μU/ml in the matched control group (p<0 05) The early serum insulin response was also significantly higher in the untreated than in the treated hypertensive group (p<0 05) When early and late serum insulin responses in the untreated hypertensives were compared with those in their weight matched controls no significant differences were found The serum insulin index was significantly lower in the treated hypertensives than in the population sample This index was similar in the untreated hypertensives their matched controls and in the population sample

Table V *Frequency (%) of low K values in untreated hypertensives and their weight matched controls treated hypertensives and in the population sample*

	K value		
	≤0 90	≤1 00	≤1 10
Untreated hypertensives	16 9	22 0	32 2
Weight matched controls	12 0	18 7	28 0
Treated hypertensives	17 5	23 8	33 3
Population sample	8 7	12 5	18 2

p<0 05 p<0 01 compared with population sample

Other laboratory investigations

Serum creatinine concentrations were the same in all four groups Only one subject previously treated for malignant hypertension had elevated serum creatinine 2 4 mg/100 ml

Finally it can be mentioned that the mean haematocrit value was 44 4±2 8% in the untreated hypertensive group and 43 6±2 3% in their weight matched controls This difference was significant ($p<0\ 05$) On the other hand there was no difference between the latter group and the population sample (43 4±2 6%)

Electrocardiogram

The resting ECG was normal in 48 (55 2%) of the untreated men and in 39 (44 8%) of those previously treated The corresponding rate in the total population was 69 7% which was significantly higher than in both the untreated ($p<0\ 01$) and the treated group ($p<0\ 001$) Only one subject in each group of hypertensives had ECG findings typical of LVH Five men in the untreated group and 8 in the treated group had signs of probable LVH The remaining pathological items reported were predominantly non specific

DISCUSSION

The BP has a unimodal distribution and there is no natural cut-off point at the right end of the distribution curve The prevalence of high BP accordingly s on the limits used to define hypertension O has recommended the level of ≥160/95 mmHg for screening purposes in population groups Using these criteria 15–20% of adults have been demonstrated to have hypertension in the United States (10 12) In Sweden 5 5% of 50-year-old men had hypertension according to the criterion of a casual BP of ≥175/115 mmHg recorded in the morning and including those on antihypertensive therapy (17) The prevalence was 11% among men aged 54–55 using the same cut off points but recording the BPs in the afternoon (22) Thus comparisons are also complicated by dissimilarities in techniques used In view of these aspects the prevalence seems to be very similar in the developed countries In the present study the prevalence was 7 5% when including those on antihypertensive treatment

In a recent report on a population study in Albury community in Australia 17 7% of the men aged 50–59 had at some time been told that they had a high BP (15) The corresponding percentage in the Uppsala study was 13 5% which was almost twice the prevalence of hypertension

In the present study half of the hypertensives were treated This agrees with observations elsewhere (15 21 22) Data from the United States have shown that 30% of the hypertensives were on treatment but only 17% under good control (21) In Uppsala 28% had a satisfactory BP control

Concerning the type of therapy 61% of the subjects used diuretics in Uppsala and 38% used β blocking agents In the Albury study the most common drugs were diuretics used by 62% and methyldopa used by 41% (15) The value of comparing drugs used in different countries is limited since the availability of drugs varies from one country to another The prescription of a drug may also vary within a country due for instance to local traditions in the choice of antihypertensive drugs

The role of inheritance in hypertension is well known In our study the frequency of a family history of hypertension was highest among the relatives of the previously treated hypertensives The reason may be that these hypertensives were examined earlier due to their awareness of the family history It is also possible that the hypertension in this group was accompanied by symptoms and thus treatment at an earlier age

Hammond et al (8) have shown that the offspring of short lived parents had a considerably higher death rate from coronary and hypertensive heart disease as well as from cerebrovascular lesion In the present study there were more dead parents in the hypertensive groups than in the population sample This is in accordance with the findings in a study of 50 year-old men where subjects with a dead father or mother had a significantly higher BP than those with their parents alive (1)

Tibblin (17) found that the proportion of smokers decreased with rising BP The present study showed the same tendency the frequency of smokers being 10% lower in the hypertensives than in the total population (Table III) In the treated hypertensives this difference was due to the fact that 36% had never smoked compared with 26% in the total population ($p<0\ 05$)

In accordance with earlier reports the hypertensives had a significantly higher relative body weight (1 17) They also had a greater subscapular skinfold thickness indicating that the difference in body weight between the untreated hypertensives

and the population sample was due to a different degree of obesity Thus the finding of elevated serum TG levels as well as of a higher frequency of reduced glucose tolerance could be explained by this overweight as there were no significant differ ences compared with the weight matched controls the only exception being the prevalence of isolated hypertriglyceridaemia

An association between obesity and serum uric acid has previously been reported (14 18) In the present study this association did not seem to be the whole explanation because untreated hypertensives with weight index ≤1 10 had significantly higher values than their weight matched controls In the literature opinions differ concerning the relation ship between BP and SUA level In a population study Evans et al (6) found no association of SUA with BP when a correction was made for body weight Others have reported a relationship be tween high arterial BP and SUA level (3 11) The importance of impaired renal function for the SUA level has been demonstrated by others (3 4) It is unlikely that in our group of mild-moderate hyper tension the renal function had deteriorated suffi ciently to explain the elevated SUA level Fur thermore there was no reason why the renal func tion should be more impaired in the group with weight index ≤1 10 than in those with >1 10 The treated hypertensives had the highest SUA value which might be explained by the use of diuretics

Another metabolic parameter studied in this in vestigation was serum insulin It is known that obese subjects have higher serum insulin concen trations in fasting state as well as during glucose tolerance tests (5 16) The early and late serum in sulin responses to i v glucose were significantly higher in untreated hypertensives compared with the population sample but not in the hypertensives compared with their weight matched controls Furthermore the serum insulin index was similar in the untreated hypertensive group the population sample and the weight matched control group This indicates that in hypertensives the early serum in sulin response was adequate for the degree of obe sity The treated hypertensives had a significantly lower insulin index implying a relative insulin deficit probably because of the use of diuretics as an antihypertensive drug

Most of the metabolic disturbances in the un treated hypertensives may be explained by obesity It has been demonstrated that there are two forms of obesity one characterized by hypertrophy of fat cells and the other by an increased number of fat cells (2) The first type is related to the caloric balance and associated with metabolic dis turbances Thus the tendency for higher fasting serum insulin level a higher frequency of hyper triglyceridaemia and lower K value in the untreated hypertensive group could possibly reflect the pres ence of the metabolically disturbed hypertrophic type of obesity in the hypertensives In this context it may be of interest to note the high frequency in the hypertensive group of a history of weight gain after the age of 30 resulting in increased fat cell size

All these findings strongly support the ad vantages of weight reduction in hypertensives not only for the BP but also for correcting the dis turbed metabolic pattern

ACKNOWLEDGEMENTS

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Treatment of Hypertension in Middle-aged Men

A Feasibility Study in a Community

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ABSTRACT In a health examination survey of 2 322 middle aged men the prevalence of hypertension, defined as supine DBP≥105 mmHg and including those on treatment was 7 5% All untreated and those inadequately treated were invited to a hypertension clinic One year s treatment in 86 men achieved a BP reduction of 29/17 mmHg in supine and 27/16 mmHg in erect position This reduction was maintained for a three year period and considered satisfactory in 80% of subjects Propranolol, alone or in combination with other agents, was used in more than 80% of the cases Special considerations in treating asymptomatic individuals are discussed

The importance of normal blood pressure (BP) for cardiovascular health is evident from prospective epidemiological studies (4) The value of reducing BP in preventing cardiovascular disease has been shown in controlled studies (6 7)

Community control of hypertension has been discussed at length in a recent WHO report (8) It has been considered inadvisable to start widespread population screening before pilot programmes have been carried out

The aim of this study was to bring mildly–moderately elevated BP in middle aged men under control The BP treatment was only one facet of a comprehensive feasibility study also aimed at influencing other risk factors for cardiovascular disease in these men derived from a cross sectional study in a community

MATERIAL

All men living in the City of Uppsala and born in 1920-24 were invited to a health examination survey conducted at the Department of Medicine University Hospital (7) A total of 2 322 men were examined giving a participation rate of 83 9% The investigation was carried out between Sept 1970 and Sept 1973

Untreated subjects with a diastolic BP (DBP)≥105 mmHg in supine position together with those already treated for hypertension were considered as hypertensives There were 174 of these subjects giving a prevalence rate for hypertension of 7 5% Eighty seven men were untreated and the same number were being treated (Fig 1) Thirty nine men (44 8%) on treatment were responding inadequately i e supine DBP≥105 mmHg Thus only 27 6% were being adequately treated out of the total sample of 174 hypertensives

Subjects with supine DBP≥105 mmHg were invited to another BP measurement at an out patient hypertension clinic (HT clinic) Nine men without treatment were not referred to this clinic for the following reasons 5 wanted their family doctor to take care of the BP 3 were sent to hospital for another investigation and one was going to move from the city Eleven subjects whose treatment was inadequate were not referred to the HT-clinic 6 did not want to interrupt a well established doctor contact 2 had other diseases requiring treatment one had recently started antihypertensive treatment and 2 did not accept the invitation for unknown reasons

A total of 106 men were invited to the HT-clinic (sample II Fig 1) Those with supine DBP≥105 mmHg at this second measurement were offered treatment If the supine DBP was <105 mmHg another BP control was performed three months later If the subject later turned out to have supine DBP≥105 mmHg he was likewise offered treatment

Seventeen men with a supine DBP≥120 mmHg were hospitalized for further diagnostic work up One was found to have secondary hypertension due to significant stenosis of a renal artery later operated upon These 17 men were then treated at the HT-clinic and are included in the study

METHODS

The participants were invited to the screening examination by letter and asked to fast and to refrain from smoking since the preceding midnight The examination started at 7 30 a m The BP was measured after 10 min rest in the

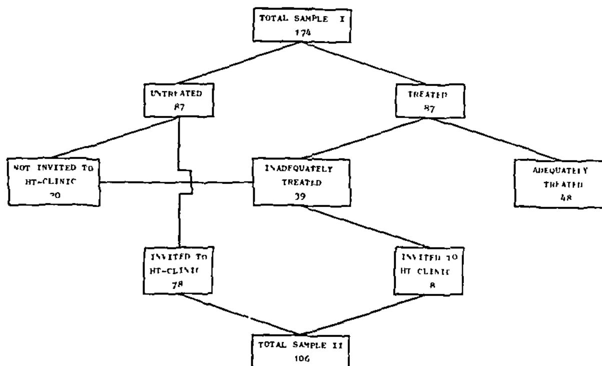


Fig 1 Descriptive flow chart over the selection of subjects for the hypertension clinic (*HT clinic*)

recumbent position using a mercury manometer (Kifa Ercameter wall model) the rubber bladder of the BP cuff being 12 5 cm wide and 35 cm long The measurements were performed on the right arm Systolic BP (SBP) and DBP were read to the nearest 5 mmHg mark The DBP was recorded when the sound had disappeared entirely (Korotkoff phase 5)

The BP measurements at the HT-clinic were performed 5 p m 4–6 weeks after the screening examination The Ps were taken by a registered nurse with the same mercury manometers and at the same department as at the screening If the subject did not come to the HT-clinic he was by letter offered a new appointment 2 weeks later The subjects were seen monthly if possible until a sufficient BP reduction had been achieved i e supine DBP<105 mmHg Thereafter the intervals were 4 months The subject always met the same physician

Propranolol (Inderal® ICI Pharma Göteborg Sweden) was given as the first drug to the subjects who were untreated The starting dose was 40 mg twice daily Each dose was increased by 40–80 mg at 2–4-week intervals up to a dose of 240 mg twice daily In those who did not obtain a DBP below 105 mmHg in the supine position the dose was given 3–4 times daily The next step was to add hydralazine (Apresolin® CIBA Mölndal Sweden) in a dose of 25 mg 3–4 times daily This dose was then gradually increased if necessary up to 200 mg daily The following step was to add diuretics

Conventional methods were used for calculating means and S D Significance of differences between means was estimated with Student s *t* test (2 tailed test) The differences between two values in the same individual were analysed with the paired observation test using the Hewlett Packard 9100 calculator program The accepted level of significance was $p<0\ 05$

Table I *Supine systolic (SBP) and diastolic (DBP) blood pressure at screening and at first visit to the hypertension clinic (HT clinic)*

	Screening			*HT-clinic*		
	n	Mean	S D	*n*	Mean	S D
SBP total	106	174 5	19 0	103	171 7	24 7
DBP total	106	111 8	7 7	103[a]	109 8	12 3
SBP untreated	78	173 7	17 6	75[a]	172 1	22 7
DBP untreated	78	111 1	7 5	75	109 7	11 8
SBP treated	28	176 6	22 7	27[b]	171 3	30 1
DBP treated	28	113 6	7 9	27[b]	110 4	13 9

[a] One drop-out and BP missing in 2 subjects [b] BP missing in 1 subject

RESULTS

BP values at the screening examination

The mean BP values of the 106 men (sample II Fig 1) who were referred to the HT-clinic are shown in Table I There were no significant differences be

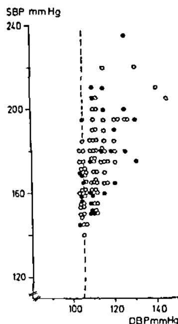


Fig 2 Distribution of supine BPs in 106 men at the screening examination =diastolic BP=105 mmHg O=untreated ●=treated subjects

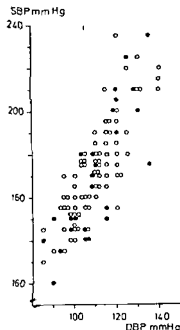


Fig 3 Distribution of supine BPs in 103 men at the HT clinic Symbols as in Fig 2

tween the average BP values at the screening and at the HT-clinic The supine BPs at the screening examination are shown in Fig 2

The relation between supine SBP and DBP in 103 men at the first visit to the HT-clinic is shown in Fig 3 (data missing in 3 subjects in 2 of them because of admission to hospital) Thirty-one men had supine DBP<105 mmHg on this occasion 24 untreated and seven treated Thirteen of the untreated subjects remained below this limit during

Table II *Blood pressures in 86 men at the initial examination and after one year s treatment*

	Initial examination			After one year			Reduction	
	n	Mean	S D	*n*	Mean	S D	mmHg	%
Supine								
SBP total	86	176 7	19 1	86	147 4	19 7	29 3	16 6
DBP total	86	112 2	7 2	86	95 8	8 8	16 5	14 7
SBP previously untreated	58	176 7	17 4	58	145 9	14 8	30 9 *	17 5
DBP previously untreated	58	111 6	6 9	58	95 0	7 8	16 7	15 0
SBP previously treated	28	176 6	22 7	28	150 5	27 3	26 1	14 8
DBP previously treated	28	113 4	7 9	28	97 5	10 6	15 9	14 0
Standing								
SBP total	83*	172 8	24 5	86	144 8	19 1	26 8	15 5
DBP total	83*	118 2	12 2	86	103 0	7 9	15 8	13 4
SBP previously untreated	56	175 8	21 1	58	143 4	14 4	31 1	17 7
DBP previously untreated	56	119 3	10 5	58	103 9	6 4	17 1*	14 3
SBP previously treated	27	166 5	29 9	28	147 7	26 4	18 0	10 8
DBP previously treated	27	115 9	15 1	28	101 1	10 2	13 5	11 6

At the HT-clinic
* Data missing on 3 subjects
* $p<0 05$ $p<0 001$ comparing previously untreated and treated groups

Table III *Blood pressures in 60 men at the initial examination and after two years of treatment*

	Initial examination			After two years			Reduction	
	n	Mean	S D	n	Mean	S D	mmHg	%
Supine								
SBP total	60	177 5	18 3	60	146 3	17 1	31 3	17 6
DBP total	60	112 8	7 7	60	94 9	8 7	17 9	15 9
SBP previously untreated	45	176 7	17 0	45	144 0	14 7	32 7[c]	18 5
DBP previously untreated	45	111 6	7 1	45	93 4	8 0	18 1	16 2
SBP previously treated	15	180 0	22 2	15	153 0	22 2	27 0	15 0
DBP previously treated	15	116 7	8 4	15	99 3	9 4	17 3	14 8
Standing[a]								
SBP total	57[b]	176 4	22 2	60	144 8	19 1	30 9	17 5
DBP total	57[b]	120 0	11 2	60	103 0	7 9	16 8	14 0
SBP previously untreated	43	175 5	20 0	45	143 1	17 5	31 6	18 0
DBP previously untreated	43	119 0	10 7	45	102 2	7 8	16 9	14 2
SBP previously treated	14	179 3	28 5	15	150 0	23 1	28 6	16 0
DBP previously treated	14	123 2	11 9	15	105 3	7 9	16 8	13 6

[a] At the HT clinic [b] Data missing on 3 subjects [c] $p<0.05$ comparing previously untreated and treated groups

one year follow up They were excluded from the following part of the study One subject did not appear at the HT-clinic Thus 92 men were included in the therapeutic part of the study

BP values after one year s treatment

Out of 92 men 86 remained after one year The initial mean BPs of these 86 men are shown in Table II together with the values after one year s treatment The average BP reductions calculated with paired *t* test in the 86 subjects were 29 3/16 5 26 8/15 8 mmHg in supine and in standing position respectively The mean BP reduction in the previously untreated group was significantly greater than in the previously treated group

The distribution of supine BPs in the 86 men after one year is shown in Fig 4 In 19 men the DBP was not below 105 mmHg The relation between supine SBPs at the screening and after one year is shown in Fig 5 In 7 subjects (8 1%) the SBP was unchanged or higher The same relation between DBPs is shown in Fig 6 Sixty eight subjects (79 1%) showed a reduction of ≥10 mmHg In 6 subjects (7 0%) the DBP was higher or unchanged

BP values after two years treatment

BP values at the initial examination and after 2 years are shown in Table III The average BP reduction was 31 3/17 9 and 30 9/16 8 mmHg in supine and standing position respectively The mean supine SBP reduction was significantly greater in the previously untreated group Fifty three men (88 3%) had a reduction of supine SBP≥10 mmHg In 5 subjects (8 3%) the SBP was unchanged or higher The corresponding rates for DBP were 83 3% and 8 3% respectively There were 12 men with a supine DBP not below 105 mmHg

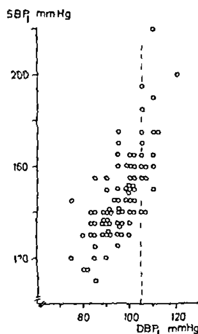


Fig 4 Distribution of supine BPs in 86 men after one year of treatment =diastolic BP=105 mmHg

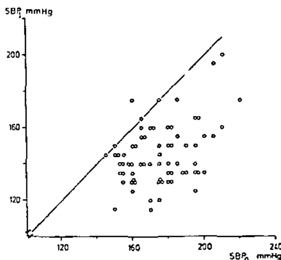


Fig 5 Relation between supine systolic BPs in 86 men at the screening examination (*SBP₀*) and after one year of treatment (*SBP₁*)

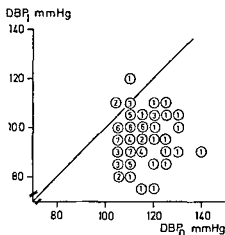


Fig 6 Relation between supine diastolic BPs in 86 men at the screening examination (*DBP₀*) and after one year of treatment (*DBP₁*) Figures in circles=no of subjects

BP values after three years treatment

So far a 3 year follow-up has been obtained in 31 subjects 9 of whom belonged to those previously treated The BPs were 145 0/93 9 in supine and 143 9/99 4 mmHg in standing position These values represent a reduction of 32 7/19 7 mmHg and 33 2/18 6 mmHg for supine and standing BP respectively A review of the BP reduction over the 3 year period is shown in Fig 7

Degree of BP control

Table IV reviews three grades of BP control referring to the supine DBP and shows the percentage of subjects with each grade Thus 22% and 20% had DBP>100 mmHg after 1 and 2 years respectively

Table V relates the DBP at the screening to the DBP after one year s treatment It can be seen that of the 19 subjects with DBP>100 mmHg 11 had an initial DBP of 105–110 mmHg On the other hand 6 out of 9 subjects with an initial DBP of ≥125 mmHg had moved below 105 mmHg

Table IV *Degree of blood pressure control after one two and three years therapy*

Supine DBP (mmHg)	1 year		2 years		3 years	
	n	%	*n*	%	*n*	%
<95	32	37 2	26	43 3	12	38 7
95–100	35	40 7	22	36 7	14	45 2
>100	19	22 1	12	20 0	5	16 1
Total	86	100	60	100	31	100

Drug therapy

In 4 subjects propranolol was never given because of contraindications asthmatic bronchitis in 3 cases and incipient heart failure in one case At the end of the first year of treatment propranolol was being used by 71 (82 6%) of the total group of 86 men it was the only drug in 33 (38 4%) The dosages are

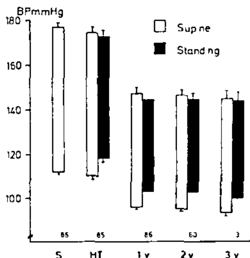


Fig 7 Supine and standing BPs at the screening (*S*) and at the first visit to the HT-clinic (*HT*) and during three years of treatment (mean±S E M)

Table V *Relation between supine diastolic blood pressure (DBP mmHg) at screening and after one year s treatment in 86 subjects*

At screening	After 1 year <95	95–100	>100	Total
105–110	21	24	11	56
115–120	7	9	5	21
≥125	4	2	3	9
Total	32	35	19	86

Table VI *Dosages of propranolol after one year's treatment*

For this study 250 mg tablets were available

Dosage (mg)	Total material (*n*) Single	Comb	Previously untreated (*n*) Single	Comb
160–250	8	14	6	4
320–480	19	18	17	14
500–1 000	6	6	5	1
Total	33	38	28	19

shown in Table VI The average daily dosage of propranolol when used alone was 406 mg and 392 mg when used in combination with other drugs

Thirty five men (40 7%) received hydralazine 31 of them in combination with propranolol The mean dosage of hydralazine was 129 mg (range 75–200) The third most commonly used drug was a diuretic given to 16 subjects (18 6%)

After 2 years the type of therapy was essentially the same as after one year Thus over 80% of the hypertensives used propranolol alone or in combination

Side effects

Three subjects developed signs of bronchospasm In 2 of them the indication for propranolol was already in doubt before the drug was started because of a suspicion of earlier bronchitis In another 2 subjects the drug was withdrawn because of complaints of diarrhoea There was another group of subjects 5 in all in whom the drug was discontinued for psychological reasons Four of them all previously untreated complained of drowsiness insomnia and uncharacteristic muscle symptoms The same subjects have later claimed that other drugs caused similar side-effects One man suffered from impotence Thus propranolol had to be discontinued in 10 out of 81 subjects who were given this drug initially Two subjects complained of vivid dreams and one had visual hallucinations before sleeping This was however easily relieved by taking the last dose earlier in the evening One subject on hydralazine therapy with previously known malignant hypertension with impaired renal function developed a SLE syndrome

Drop-outs

A total of 8 subjects (7 5%) dropped out over the 3 year period Three men died one from myocardial infarction one from injuries received in an accident and the third committed suicide This man was depressed after an accident which caused invalidity there was no reason to believe that the depression was drug induced Two men had known alcohol problems Three subjects dropped out for no apparent reason after 4 8 and 16 months respectively

DISCUSSION

In the present study the arbitrary BP limit used for starting antihypertensive treatment was restricted to supine DBP≥105 mmHg It was based originally on results from the Veterans Administration (VA) study (6) which showed the benefit of antihypertensive treatment at least down to this DBP level However in the VA study the DBPs were recorded between the fourth and sixth day of *hospitalization Thus 105 mmHg in the VA study* cannot be translated to an ambulatory DBP of 105 mmHg in our study Later studies have shown SBP to be as good a predictor of cardiovascular complications

The BP measurements at the HT-clinic were taken in the afternoon while the screening BPs were recorded in the morning The regular increase in BP during the day was not observed here It was probably counteracted by an adaptation to the examination procedure by the second visit

At the first visit to the HT-clinic 31 men had supine DBP below 105 mmHg illustrating the variability of the BP as well as the statistical phenomenon of regression towards the mean Seven of them were previously treated and the reduced BP level

could possibly reflect an improved adherance to prescribed medication

The BP reductions over the years can be considered acceptable in view of the special problems faced in this kind of study They were of almost the same magnitude as those reported in some clinical studies using β blocking agents (1 9)

After 1 and 2 years about 20% of the subjects had not become normotensive i e their supine DBP was not below 105 mmHg Different ways can be used to evaluate the degree of BP control ascertained The most informative is to relate the BPs under treatment to the initial BP level as illustrated in Table V

Concerning the individual results many subjects had a good BP reduction (Table V) However there were 19 in whom it was unsatisfactory and a few comments are called for on this group There were 11 previously treated men among these non responders and even their screening BPs may have represented a considerable reduction of the initial level This group of previously treated men also had a more impressive family history of cardiovascular disease as well as hypertension (3) Finally it is of course possible that they did not follow the recommended medication or dosage schedule In several subjects this was supported by the observation that the BP was out of control accompanied by a higher pulse rate than usually seen in that subject as well as in a patient on a β receptor blocking agent

Despite the insufficient BP reduction in some individuals there were psychological obstacles that prevented an increase of the daily dosage or the addition of another drug For example in an asymptomatic subject there might be a tendency to blame the new regimen diet or drug for every conceivable complaint that arose during the trial One then has to take considerable pains to inform the individual of the risks and gradually to improve the motivation for more effective treatment In some cases there were also practical difficulties in seeing the subjects at the HT-clinic sufficiently often to obtain good BP control within a reasonable time

Propranolol was used as the first drug the reason being its well documented antihypertensive effect relative lack of side-effects and simple mode of administration—twice a day (1 5 9)

The number of subjects who had to discontinue the β blocking agent due to apparent drug induced side-effects were few The therapy had to be changed for psychological reasons in the same number of subjects because of uncharacteristic symptoms probably not drug related This illustrates the well known observation that untreated hypertensives have few symptoms but treated ones have considerably more At the same time it is important to be on the alert for possible side-effects when introducing a drug to healthy individuals

Among factors of importance for the drop-out in this kind of study a low frequency of side effects may be of significance Other positive factors according to the opinions expressed by the participants were the late afternoon time for the HT clinic and that they always met the same doctor In spite of the small number of drop-outs there was a tendency for these to occur early in the follow up Our small material does not allow any further conclusions

When discussing the drop-out rate another aspect should be emphasized At screening in a community there are individuals who prefer their regular doctor to take care of any abnormal findings This is illustrated by the 11 men (8 8%) who stated that they wanted to consult their own doctor This number was similar to the drop-out rate over 3 years However the few drop-outs over the years as well as the high participation rate in this type of health examination indicate that middle aged men are highly concerned about their health

When attempting to modify the risk factor pattern in asymptomatic individuals there are very particular aspects to consider In conventional medicine the subject is a patient seeking medical advice because of a feeling of sickness or concern about disease in his family or surroundings In a primary preventive trial the doctor has to convince the subject that attempts should be made to change factors of risk of which he has been unaware Furthermore the individual has to be motivated for perhaps life long treatment and follow up Certainly there is a substantial risk of causing discomfort and anxiety in the individual The situation is still more complex when dealing with more than one risk factor There have been great difficulties in superimposing effective anti smoking and lipid lowering programmes on the antihypertensive therapy

All these aspects must be considered when evaluating the therapeutic results of primary preventive trials It should also be stressed that in such a study the main purpose is not to evaluate the efficiency of a pharmacological agent

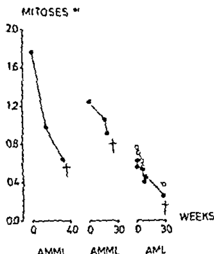


Fig 1 Mitotic indices during the course of illness in cases 1 2 and 3 with acute myeloid leukaemia ●=all granulopoietic precursors ○=myeloblasts separately

was negative Serum B_{12} 3410 ng/l A detailed case report with a chromosome analysis is given by Mitelman et al (8) A mitotic study has been reported elsewhere (15)

Chronic myeloid leukaemia (CML)

Case 6 (Fig 3) The patient is a 30-year old woman with a Ph¹ positive type of CML Her initial blood data were Hb 12 8 g/100 ml WBC 22400 and platelets 280000 She did well for 3 years and received no treatment On Aug 15 1973 the Hb was 9 7 g/100 ml WBC 385000 and platelets 400000 In Sept 1973 she was treated with Myleran® and is still alive A case report is given by gren (13)

Case 7 (Fig 4) This patient was a 74 year old man with Ph¹ negative type of CML (2 7) His initial blood data ere Hb 8 0 g/100 ml WBC 27700 and platelets 205000 He was studied for 75 weeks with increasing WBC and severe thrombocytopenia At the end of this period the patient developed a blastic crisis with WBC 90000 and 4000 platelets He died within a week and the autopsy verified the initial diagnosis

MATERIAL AND METHODS

Examination of bone marrow smears Bone marrow was obtained by conventional sternal puncture and smears were stained with May-Grunwald-Giemsa A differential count of 1000–3500 nucleated cells was performed and the cells were classified according to Heilmeyer and Begemann (4) and Sjögren (13) A mitotic index of the granulopoietic precursor cells (myeloblasts promyelocytes and myelocytes) was calculated from an examination of 4650–42650 such cells In two cases of AMML the monocytic precursor cells (13) were included in the group of precursors In some cases with a high frequency of myeloblasts separate mitotic indices were determined

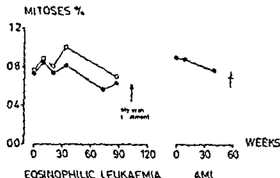


Fig 2 Mitotic indices during the course of illness in case 5 with eosinophilic leukaemia and case 4 with acute myeloblastic leukaemia

for the myeloblasts and the myelocytes Because of the nuclear and cytoplasmic asynchrony of the granulopoietic precursors it was very difficult to separate the promyelocytic and myelocytic mitoses Therefore these cells were pooled to form a single group

RESULTS

The mitotic indices during the course of illness of the seven patients are presented in Figs 1–4 The mean values of the mitotic indices of the granulopoietic precursors in four normal materials vary between 1 0 and 1 2% (6 9 12 13)

The slopes of the mitotic curves were correlated to the survival time $r_s=0.86$ $p<0.05$ (the Spearman rank correlation coefficient) The lines of best fit were determined by the method of least squares

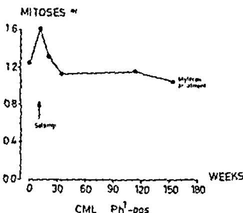


Fig 3 Mitotic indices during the course of illness in case 6 with Ph¹ positive chronic myeloid leukaemia

DISCUSSION

It is well documented that leukaemic blast cells have a low proliferative activity (2 3 5 13–18) The reduced activity has been attributed as a rule to the myeloblasts—for a review see Killmann (5)—but some recent investigations on rather specific forms of myeloid leukaemias e g monocytic (18) promyelocytic (14 18) and eosinophilic (15) have provided evidence that the mitotic indices of the promyelocytes and monocytic precursors are also low It is interesting that the lowest indices were found in acute promyelocytic leukaemia i e the type of leukaemia with the shortest survival Brandt et al (2) have shown that the mitotic indices of the granulopoietic precursors were significantly lower in *CML* patients without the *Ph[1]* chromosome than in those with that chromosome Up to now it has not been possible to assert a prognostic value of mitotic studies for any of the myeloid leukaemias regardless of type Besides Brandt et al (3) found no relation between *chromosomal abnormalities* and mitotic activity in 15 cases of acute myeloid leukaemia

In the present study the mitotic indices declined during the course of illness in all seven cases Occasionally high mitotic indices could be explained by superposed infections (14) During the studies the proportion of myeloblasts increased continuously but the depressed mitotic activity could not be the result of such a shift to the left within the granulopoiesis since the normal myeloblasts are known to have higher mitotic indices than the myelocytes (6 9 12) In case 7 (Fig 4) the decline in mitotic indices could be attributed to the myeloblasts alone but in two other cases (nos 3 and 5 Figs 1*c* and 2*a*) there was a concomitant decline in the mitotic indices of the myelocytes

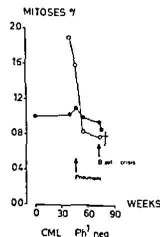


Fig 4 Mitotic indices during the course of illness in case 7 with Ph[1] negative chronic myeloid leukaemia

Although it is evident that leukaemic cells are rather heterogeneous with respect to their kinetic behaviour low mitotic indices of the granulopoietic precursor cells indicate leukaemic involvement of *these cells Repeated* mitotic studies seem to give valuable diagnostic and prognostic information especially in patients in whom karyotype analyses show normal conditions

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Distribution of Immunoglobulin-containing Cells in Human Bone Marrow and Lymphoid Tissues

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ABSTRACT Cell suspensions of human bone marrow, spleen, lymph nodes and palatine tonsils have been investigated for the presence of intracellular immunoglobulins by a direct immunofluorescence technique, using monospecific antisera against human Ig heavy chains α, μ and γ and light chains κ and λ Serum Ig levels were determined and the number of positive cells was compared with the concentration and calculated synthetic rate of serum Ig in each individual The 28 patients studied covered a wide range of diagnoses and included those with normal as well as pathologically decreased or increased serum Ig levels There was a high correlation between the calculated synthetic rate of each Ig class and the percentage of cells positive for the same Ig class in the bone marrow but not in the spleen lymph nodes or tonsils The Ig-containing cells constituted a much larger proportion of the total lymphoid cell population in the bone marrow than in the peripheral lymphoid organs The estimated total number of Ig containing cells was also much larger in the bone marrow than in the other organs investigated It is concluded that in man the bone marrow is the major site of serum Ig synthesis and that the average synthetic rate per cell is the same regardless which of the three major Ig classes is produced The role played by different lymphoid organs in humoral immunity is discussed in the light of the present results and reported data regarding lymphocyte and plasma cell kinetics in mammals

Since the early observations by Bing and Plum (10) Bjorneboe and Gormsen (11) and Fagraeus (20) the role of plasma cells and large and medium sized lymphocytes in antibody synthesis has been documented by a large number of investigators The methods used include techniques for detection and quantitation of antibody produced by a single cell in vitro (3 39) secretion of immunoglobulins by suspension cultures of bone marrow and lymphoid tissue (2 22) and demonstration of intracellular immunoglobulin by immunofluorescence and/or immunoenzymatic staining (4 22 44)

Immunoglobulin producing cells are seen mainly in the bone marrow spleen lymph nodes blood and the lymphoid tissue of the gut and respiratory tract and may infiltrate other tissues in inflammatory processes (9) The relative contribution of different lymphoid organs to antibody synthesis has been studied to some extent in animals Askonas and Humphrey (1) followed γ globulin production *by guinea pig tissues using ovalbumin as the* antigenic stimulus They considered the bone marrow to be the most important organ for antibody production even though the antibody activity per unit tissue was highest in the spleen after primary i v immunization and in the regional lymph node after intradermal immunization Similar results were obtained by Mellbye (43) who investigated the primary immune response in mice using the hemolytic placque technique On the other hand Eidinger and Pross (19) did not observe any significant activity in the bone marrow using the same experimental model Comparative studies in man are few McMillan et al (42) investigated immunoglobulin synthesis by human lymphoid tissues in vitro and found the bone marrow to be a major site of serum IgG production

The aim of the present investigation was to evaluate the role of different human lymphoid organs in the synthesis of serum immunoglobulins by studying their content of immunoglobulin producing cells Bone marrow lymph nodes splenic and tonsillar tissues were examined by an immuno-

Table I *Distribution of Ig containing bone marrow cells by Ig classes and number of cells positive for IgA IgM or IgG/1 000 nucleated cells Comparison between bone marrow from sternum (STP) and iliac crest (CRP)*

κ/λ=ratio κ positive cells/λ positive cells H/L=ratio cells positive for heavy chains/cells positive for light chains n d =not done

Case no		Ig-containing cells (%)					Positive cells per 1 000 nucleated cells		
		IgA	IgM	IgG	κ/λ	H/L	IgA	IgM	IgG
1	STP	39	3	58	1 5	1 3	n d	n d	n d
	CRP	33	3	64	1 5	0 9	n d	n d	n d
2	STP	9	9	82	1 6	1 4	3 9	3 9	40
	CRP	9	9	82	2 2	n d	n d	n d	n d
3	STP	38	3	59	2 1	n d	18 1	1 4	28 2
	CRP	38	7	55	1 9	1 0	19 5	3 6	28 2
4	STP	32	5	63	1 4	1 1	n d	n d	n d
	CRP	35	1	64	1 4	1 0	15 4	0 4	28 1
5	STP	52	11	37	n d	n d	14 2	3 0	10 1
	CRP	51	12	37	1 3	n d	17 3	4 1	12 5

fluorescence technique for the presence of cells with intracellular immunoglobulins The percentage of cells positive for the different immunoglobulin classes was compared with the synthetic rate of serum immunoglobulin classes in each individual and the total number of immunoglobulin producing cells in the lymphoid organs was estimated

MATERIAL

… marrow was aspirated from the sternum and/or the …iac crest of 28 patients with miscellaneous diagnoses and varying concentrations of serum Ig The following diagnoses were represented rheumatoid arthritis (n=3) essential polyclonal hypergammaglobulinemia (n=3) liver cirrhosis (n=3) pernicious anemia (n=2) acute leucemia (n=2) Crohn s disease (n=2) chronic active hepatitis Sjogren s disease chronic glomerulonephritis chronic bronchitis cervical lymphadenitis osteoporosis and sideropenic anemia bronchial carcinoma chronic pancreatitis and arthralgias cardiosclerosis erythema annulare centrifugum recurrent respiratory infections Hodgkin s disease and high ESR (one of each)

Splenic tissue was obtained at abdominal surgery in 10 cases The spleen was removed for technical reasons in operation for renal cancer (n=2) renal arterial stenosis (n=2) vagotomy in duodenal ulcer (n=1) and shunt operation in liver cirrhosis with portal hypertension (n=1) Splenectomy was performed in one case of idiopathic thrombocytopenia one case of thrombocytopenia secondary to radiological therapy for cancer of the urinary bladder and in one case of sarcoidosis and thrombocytopenia Splenectomy was performed for staging in one case of Hodgkin s disease

Inguinal lymph nodes were obtained at operation for varicose veins in five cases Mesenteric lymph nodes were taken in the course of operation for Crohn s disease (n=2) vagotomy (n=1) splenectomy in sarcoidosis with thrombocytopenia (n=1) One lymph node came from a patient with a cervical lymphadenitis Tonsillar tissue was obtained in 7 cases with tonsillectomy for recurrent tonsillitis

Serum was taken on the day when tissue was obtained or in some cases the day after Patients with a monoclonal gammapathy judging by agarose gel electrophoresis were not included in the study neither were patients with evidence of major urinary protein losses

METHODS

Immunofluorescence

The methods used were essentially those described by Hijmans and Schuit (36) and Vossen (58) Single cell suspensions were prepared from bone marrow by shaking marrow fragments on a mixer and from lymphoid tissue by grinding through a metallic wire mesh using a Borel mincer after careful removal of capsule and fat In the spleen cell preparations red cells were lysed with 0 15 M NH_4Cl for 5 min at room temperature After careful washing of the cells slides were prepared using a cytocentrifuge which allows the preparation of a series of slides containing approximately the same number of cells from the same cell suspension spread over equally large areas After fixation in 95% ethanol 5% acetic acid at −20°C for 15 min followed by repeated washings successive slides were stained with FITC (fluorescein isothiocyanate) or TRITC (tetramethylrhodamine isothiocyanate) conjugated antisera aginst human Ig heavy chains α μ and γ (Nordic Immunological Laboratories Tilburg Holland) and light chains κ and λ (gift from W Hijmans Rijswijk

Table II *Serum Ig concentrations and distribution of serum Ig synthesis and Ig containing bone marrow, lymph node, spleen or tonsil cells by Ig classes*
Abbreviations as in Table I

	Serum concentration (g/l)			Calculated serum Ig synthesis (%)			Ig-containing cells (%)				
	IgA	IgM	IgG	IgA	IgM	IgG	IgA	IgM	IgG	κ/λ	H/L
Bone marrow (N=28)											
Mean	2.7	2.9	14.6	30	14	56	30	15	55	1.5[a]	1.1[b]
S.D.	1.8	3.2	6.2	15	13	18	14	16	17	0.3	0.2
Range	0.1–8.4	0.3–14.0	9–29	1–52	1–57	28–97	1–52	1–70	19–55	1.2–2.1	0.9–1.6
Lymph nodes (N=10)											
Mean	2.3	1.2	11.0	38	8	54	11	23	66	1.5	1.0
S.D.	0.6	0.6	2.5	8	5	7	5	8	7	0.2	0.2
Range	1.3–3.6	0.7–2.5	6–15	24–52	3–14	42–63	4–20	14–41	55–73	1.2–1.7	0.9–1.4
Spleen (N=10)											
Mean	2.5	1.3	9.8	42	10	48	21	20	59	1.6	1.1
S.D.	1.1	0.9	4.5	14	8	11	7	15	15	0.3	0.1
Range	0.4–4.3	0.4–3.2	4–16	27–60	5–32	35–63	12–31	5–46	32–77	1.4–2.2	1.0–1.3
Tonsils (N=7)											
Mean	2.3	1.1	11.1	35	8	57	30	9	61	1.4	0.9
S.D.	1.0	0.6	2.7	8	4	10	10	3	11	0.3	0.1
Range	0.7–3.9	0.5–2.0	9–17	20–45	6–14	51–74	19–41	5–13	47–74	1.1–1.8	0.7–1.1

[a] *N*=26. [b] *N*=25. [c] *N*=9.

Holland). The specificity of the conjugates was tested before use by immunodiffusion techniques and performance testing on myeloma and macroglobulinemia bone marrow slides (35). TRITC conjugated bovine serum albumin was used as a counter stain. The slides were mounted in buffered glycerol (9 parts glycerol to 1 part 0.01 M phosphate buffered saline pH 7.8) and sealed with paraffin wax. In each case one slide was Pappenheim stained. One conventional smear made from part of the aspirated bone marrow was also Pappenheim stained. Sections of lymph nodes and spleens were stained with hematoxylin and eosin. They were examined at the Department of Clinical Pathology (A. Rausing).

The slides were examined with a Leitz Orthoplan fluorescence microscope with an HBO 100 lamp as light source and epillumination and filter systems for the two wavelength method (34). Cells showing cytoplasmic fluorescence were identified and the number of positive cells in each slide or in a defined central section of each slide was determined. The number of nucleated cells was determined in the Pappenheim-stained slide. The following calculations were made: the percentage of Ig containing cells positive for IgA, IgM or IgG, respectively, the ratio of κ positive to λ positive cells (κ/λ ratio), the ratio of cells positive for heavy chains/cells positive for light chains (H/L ratio) and the frequency of cells positive for IgA, IgM or IgG expressed as cells/1000 of all nucleated cells in the preparation.

Serum immunoglobulins

The serum concentrations of IgA, IgM and IgG were determined by electroimmunoassay (25, 41).

The examinations were performed at the Department of Clinical Chemistry (A. Grubb). Average values for fractional catabolic rate (FCR) of Ig classes were taken from the literature. FCR is expressed as the fraction of the circulating pool catabolized daily and gives a correct value for the total catabolic rate irrespective of whether extravascular catabolism takes place or not (59). For IgA an average FCR of 0.252 has been reported (55) and for IgM 0.106 (38). The FCR of IgG is influenced by the serum IgG

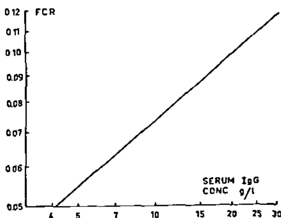


Fig. 1. IgG fractional catabolic rate as a function of serum IgG level. Recalculated from Waldmann and Strober (59) using a logarithmic scale for both axes.

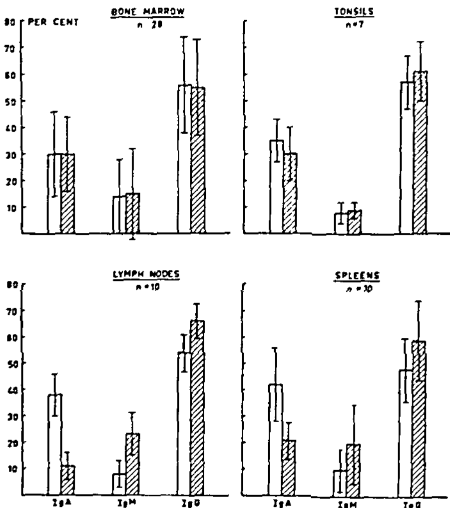


Fig 3 Distribution of serum Ig synthesis and Ig containing bone marrow tonsil lymph node or spleen cells by Ig classes Mean and S D for IgA IgM and IgG in each group ☐=calculated percentage of serum Ig synthetic rate ▨=percentage of Ig containing cells

and to calculate the FCR in each individual data given by Waldmann and Strober (59) were used g 1) The amount of IgA IgM or IgG catabolized daily in each individual was then calculated as the product of serum concentration a constant representing the plasma volume and the FCR Assuming a steady state with daily synthesis equal to daily catabolism it was thus possible to compare the synthetic rate of the three major Ig classes and express the synthetic rate of each Ig class as a percentage of the total serum Ig synthetic rate

Statistical evaluations were made using the *t* test for paired observations and for linear regression

RESULTS

Examination of histological sections of lymph nodes and spleens stained with hematoxylin and eosin showed a rather wide variation in the development of specific lymphatic parenchyma germinal centers and plasma cell occurrence The material included both some inactive partly fibrotic lymph nodes and some clearly activated nodes with plasma cell increase In the two lymph nodes from patients with Crohn s disease epithelioid granulomas were seen In the cases of renal cancer and Hodgkin s disease where splenectomy was performed there were no signs of tumour growth in the spleen

Cytocentrifuge slides from bone marrow cell suspensions showed a cell distribution similar to conventional smears with a lymphoid cell content of about 20% The plasma cell percentage was however always about twice as high as in smears It was in good agreement with the percentage of Ig containing cells as determined by immunofluorescence and was considered to be the more representative figure when used for comparison with the frequency of Ig containing cells in cell suspensions from lymphoid tissue prepared in the same way The cell suspensions obtained from tonsils and lymph nodes consisted mainly of

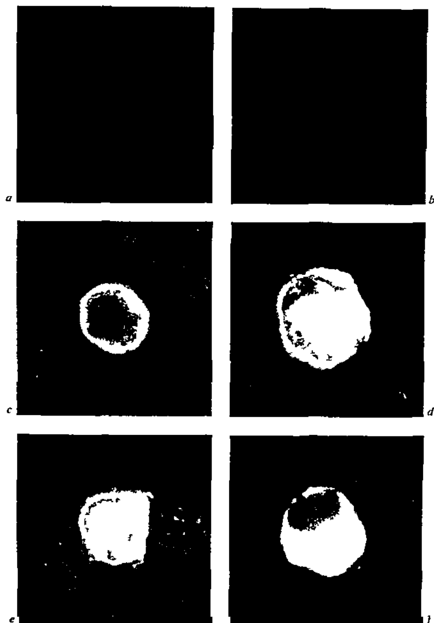


Fig 2 Cytoplasmic fluorescence in plasma cells and differentiated lymphocytes Cytocentrifuge slides stained with fluorescent antisera against human Ig chains (*a*) Plasma cell stained with anti κ FITC Bone marrow (*b*) Plasma cell stained with anti λ TRITC Bone marrow (*c*) Medium-sized lymphocyte stained with anti γ FITC Lymph node (*d*) Large lymphocyte stained with anti μ FITC Spleen (*e*) Large lymphocyte stained with anti λ TRITC Spleen. (*f*) Plasma cell stained with anti-γ FITC Spleen (Excitation of FITC at 500 nm excitation of TRITC at 546 nm microphotography on GAF 500 colour film and Kodak tri X Pan black and white film (*a*) 800 (*b–f*) 1 100)

Table III *Serum Ig concentrations and number of Ig containing bone marrow, lymph node, spleen or tonsil cells/1 000 nucleated cells*

In 4 cases in the bone marrow group, 2 in the lymph node group and 1 in the tonsil group, the number of positive cells/1 000 nucleated cells was not calculated

	Serum concentration (g/l)			Ig-containing cells/1 000 cells			
	IgA	IgM	IgG	IgA	IgM	IgG	IgA+IgM+IgG
Bone marrow (N=24)							
Mean	2.5	3.1	14.1	9.1	4.2	16.8	30.1
S.D.	1.5	3.3	5.6	6.1	5.5	8.8	12.1
Range	0.1–5.2	0.3–14.0	9–28	0.1–23.8	0.4–24.6	5.6–36.9	9.5–59.8
Lymph nodes (N=8)							
Mean	2.4	1.3	11.5	0.1	0.1	0.4	0.6
S.D.	0.5	0.6	1.9	0.1	0.1	0.3	0.5
Range	2.0–3.6	0.7–2.5	11–15	0.01–0.3	0.02–0.3	0.1–1.0	0.2–0.8
Spleen (N=10)							
Mean	2.5	1.3	9.8	0.9	0.9	2.5	4.4
S.D.	1.1	0.9	4.5	0.7	1.0	1.6	2.5
Range	0.4–4.3	0.4–3.2	4–16	0.7–2.5	0.3–3.2	0.6–5.9	0.8–7.0
Tonsils (N=6)							
Mean	2.5	1.3	11.5	0.7	0.2	1.6	2.5
S.D.	0.8	0.6	2.8	0.4	0.2	1.3	1.8
Range	1.6–3.9	0.5–2.0	9–17	0.2–1.3	0.1–0.5	0.6–4.1	0.9–5.5

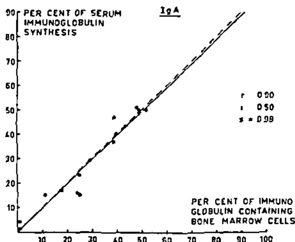
lymphoid cells (approximately 85 % and 90 %, respectively) and the spleen cell suspensions contained an average of 75 % lymphoid cells. The methods used for preparation of cell suspensions probably give an underrepresentation of fibroblasts, vascular endothelium and reticulum cells. The morphological classification of cells in Pappenheim stained cytocentrifuge slides was sometimes difficult. The frequency of Ig containing cells in the individual cases was therefore calculated as positive cells/1 000 nucleated cells rather than lymphoid cells.

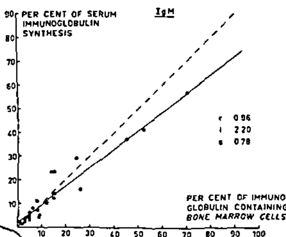
Cells showing a homogeneous cytoplasmic fluorescence were regarded as positive. The majority of positive cells were identified, using the counter stain, as plasma cells but there were also positive large and medium sized lymphocytes and these tended to be relatively more common in the lymph node and spleen cell preparations than in the bone marrow (Fig. 2). It should be stressed, however, that this morphological classification is somewhat arbitrary, as there was a gradual increase in the amount of cytoplasm from a medium sized lymphocyte to plasma cell. In the tonsils, lymph nodes and spleens there were also some small lymphocytes positive mainly for IgM. They had only a narrow rim of cytoplasm when viewed in contrast staining and the fluorescence was considerably weaker. They were not included in the calculation of the cell distribution patterns.

In five cases, bone marrow from different locations in the same patient was examined. The results are given in Table I. There is good agreement between sternal marrow and iliac crest marrow in the distribution pattern of Ig containing cells.

The results from examinations of bone marrows, spleens, lymph nodes and tonsils are given in Tables II and III. In the bone marrows an average of 30 % of Ig-containing cells were positive for IgA, 15 % for IgM and 55 % for IgG. The κ/λ ratio was 1.5 and the H/L ratio 1.1. The tonsils showed a similar distribution pattern and an H/L ratio of 0.9. In the spleens and lymph nodes the percentages of IgA positive cells were considerably lower than in the bone marrow. Both lymph nodes and spleens also had relatively more IgM positive cells and the lymph nodes more IgG positive cells.

In the bone marrow group there was close similarity between the cellular distribution pattern and the calculated distribution of serum Ig synthetic rate by Ig classes (Fig. 3). In the lymph node group the percentage of IgA-positive cells was significantly lower ($p<0.001$) and the percentages of IgM and IgG positive cells significantly h





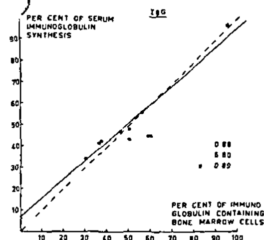


Fig 4 Calculated synthetic rate of IgA IgM and IgG in 28 patients with varying serum Ig levels expressed as a percentage of total serum Ig synthesis and compared with the percentage of Ig-containing bone marrow cells positive for the same Ig class ---$x=y$

($p<0\ 001$ $p<0\ 005$) than the corresponding values for the calculated part of serum Ig synthesis The same applied to the spleen group but here the difference was statistically significant only for IgA positive cells ($p<0\ 005$)

In Fig 4 the individual values for the percentages of Ig synthesis and Ig containing bone marrow cells are compared for each Ig class There is a high positive correlation for all three Ig classes (IgA $r=0\ 90$ $p<0\ 001$ IgM $r=0\ 96$ $p<0\ 001$ IgG $r=0\ 88$ $p<0\ 001$) No significant correlations were observed in the spleen lymph node or tonsil groups It must be pointed out however that these groups were smaller than the bone marrow group

The number of Ig containing cells per 1 000 of the total cell population was much larger in the bone marrow (mean 30 1) than in the spleen (mean 4 4) lymph nodes (mean 0 6) or the tonsils (mean 2 5) This is true for all three Ig classes (Table III) In the bone marrow group there was a high positive correlation between the number of cells positive for IgA or IgM and the serum concentrations of the same Ig classes (IgA $r=0\ 91$ $p<0\ 001$ IgM $r=0\ 94$ $p<0\ 001$) (Fig 5) As the FCR of IgA and IgM is independent of the serum level the synthetic rate is *directly proportional to the serum concentration In* the case of IgG the number of positive cells was compared with the product of serum concentration and FCR to get a theoretically linear regression as FCR is dependent upon serum IgG level (IgG $r=0\ 79$ $p<0\ 001$) As the plasma volume was not determined the total intravascular Ig pool could not be calculated Differences in individual plasma volumes may account for some of the variation observed All regression lines have intercepts above the origin which is compatible with some synthetic activity outside the bone marrow The size of this synthesis is difficult to estimate owing to the statistical errors of the intercepts Again no significant correlations were observed in the spleen lymph node or tonsil groups If the number of positive *cells/1 000 bone marrow cells is corrected* to be valid for normal serum Ig concentrations (serum Ig levels in 170 healthy adults IgA 1 8 g/l IgM 1 0 g/l IgG 10 g/l) the following figures are obtained IgA 5 8 IgM 0 7 IgG 8 8 The corrected number of IgA and IgG containing cells is still considerably larger in the bone marrow group while that of IgM containing cells is of the same size as in the spleen group but larger than in the lymph node and tonsil groups

DISCUSSION

Two approaches have been used in this study to evaluate the role of different lymphoid organs in serum Ig synthesis The distribution pattern of Ig containing cells has been compared with the calculated distribution of serum Ig synthesis by Ig classes in each individual case The frequency of Ig containing cells in different organs has been determined and the total number of Ig containing cells in each organ system has been estimated It must be borne in mind that the calculations involve several approximations The serum Ig synthesis is not known in the individual case and average figures for the FCR of Ig classes have been used Abnormalities in Ig metabolism have been reported e g in rheumatoid arthritis (50) It is thus conceivable that individual FCR values depart considerably from the average On the other hand it has been shown that the FCR of IgA and IgM is independent of the serum concentration and remains the same in patients with pathologically decreased or increased serum levels (59) The values used for FCR of IgG have been corrected according to the known variation with serum IgG level (59) A further justification for the approximation is that the cases studied cover a wide range of diagnoses The serum Ig concentrations at a particular time depend upon the synthetic activity of immunocytes during a preceding period the length of which varies with the Ig class It has been assumed that no major changes in the number or distribution pattern of Ig producing cells took place during that time While the bone marrow and spleen preparations probably are representative for these organs as a whole this might not be the case for the lymph nodes The relative number of Ig secreting cells in a lymph node can vary considerably depending upon the degree of antigenic stimulation and upon the localization and the rather small number of lymph nodes might not be representative A certain degree of plasma cell proliferation in chronically inflamed tissue is probable in some of the patients with increased serum Ig levels Furthermore it is possible that the synthetic rate of Ig-containing cells differs in different organs or between Ig classes With these reservations in mind it is however possible to draw some conclusions regarding the major sites of serum Ig production

Ig synthesis by human bone marrow cells has been documented in a number of reports van Furth et al (23) in short time culture of tissue fragments found synthesis of IgA IgM and IgG Immunofluorescent staining of cell suspensions demonstrated cytoplasmic fluorescence positive for IgA IgM and IgG in plasma cells Douglas et al (18) reported 66% of Ig containing bone marrow cells to be positive for IgG 22% for IgA and 12%

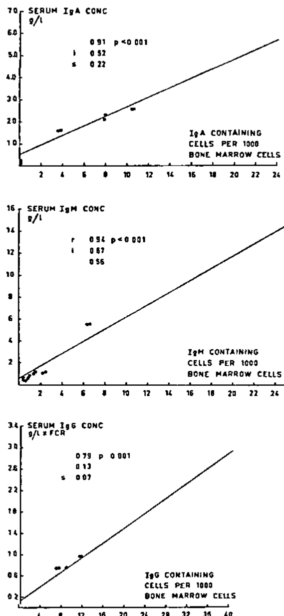


Fig 5 Serum IgA and IgM concentrations product of serum IgG concentration and FCR and number of cells positive for the same Ig classes/1 000 nucleated bone marrow cells in 24 patients with varying serum Ig concentrations

for IgM Hijmans et al (34) in a large series of bone marrow samples found 37% cells positive for IgA 12% for IgM and 51% for IgG a κ/λ ratio of 1 5 and an H/L ratio of 1 2 They did not report on serum Ig concentrations If our figures are corrected for normal serum Ig levels (IgA 1 8 g/l IgM 1 0 g/l IgG 10 g/l) the distribution pattern is IgA 35% IgM 8% IgG 57% κ/λ ratio 1 5 H/L ratio 1 1 which is in good agreement with Hijmans et al Similar re sults were reported by Vossen (58) who also found 3% IgD positive cells

Immunofluorescence studies of Ig containing cells in human spleens have given somewhat con tradictory results Chiappino and Pernis (14) found a dominance of IgG cells over IgM cells (roughly 90% and 10% respectively) in the red pulp of two spleens Bernier and Cebra (7 8) found a slight dominance of γ positive cells and a κ/λ ratio of 1 6 Similar results were reported by Chen (12) On the other hand Diebold et al (16) in a study of 17 spleens found predominantly IgM producing cells some IgG and a few IgA producing All these studies were made on sections or imprints of spleens van Furth et al (23) observed in vitro synthesis of IgG IgA and somewhat less IgM and immunofluorescence staining of cell suspensions revealed brightly fluorescent plasma cells and medium sized lymphocytes positive for IgA IgM and IgG as well as many weakly fluorescent small lymphocytes positive for IgM Our results thus dif mainly from those of Diebold et al The dis ancies might be explained by differences in the erial and technique While the use of cell uspensions has the disadvantage of ruling out top ographical localization of the cells and carries the risk of selective cell loss the main advantages are more effective washing of cells with less back ground staining and more precise quantitation

Another approach to the question of Ig produc tion in human spleens was used by Mondorf et al (45) who studied serum Ig levels in patients after splenectomy and found a decrease in IgM but not in IgA or IgG as compared with normal controls Their results point to an important role for the spleen in generation of IgM producing cells but do not necessarily imply that these remain in the spleen during IgM synthesis and secretion

Bernier and Cebra (7) stained imprints of lymph nodes obtained at surgery or autopsy with antisera against γ κ and λ chains and found about 60% γ positive cells and a κ/λ ratio of 1 9 A slight pre ponderance of IgG positive cells was also ob served by Chen (12) who examined sections of 11 mesenteric lymph nodes taken at surgery or au topsy van Furth et al (23) in mesenteric and ret roperitoneal lymph nodes from eight patients found medium sized and large lymphocytes and plasma cells positive for IgG IgA and IgM They also observed in vitro synthesis of mainly IgG but also of IgA and IgM Our results are thus in good agreement with earlier reports

In immunohistochemical studies of human na sopharyngeal tonsils Crabbé and Heremans (15) found predominantly γ positive cells also many α positive but few μ and δ positive cells Com posed with other lympoid organs the tonsils were however relatively rich in cells containing δ chains Chen and Izui (13) found γ positive cells to be the most frequent in palatine tonsils followed by α positive and μ positive Similar results in both palatine and nasopharyngeal tonsils were reported by Diebold and Nezelof (17) and by Ishikawa et al (37) who also found some IgD positive and a few IgE positive cells All these studies were done on chronically inflamed tonsils In four normal tonsils Chen and Izui (13) found a slight preponderance of IgA containing cells Our distribution figures are similar to those reported earlier We did not ex amine the cells for the presence of δ or ε chains but observed a lower H/L chain ratio than in other tissues which is compatible with the presence of a cell population positive for IgD or IgE

Hijmans et al (34) observed a striking similarity between the distribution pattern of Ig containing bone marrow cells and of serum Ig synthesis and concluded that the average synthetic rate per cell is the same regardless of which of the three major Ig classes is synthesized This observation is con firmed and extended in the present study The κ/λ ratio of the cells is in good agreement with the corresponding ratio of serum Ig which has been reported to be 1 8 (21) For each Ig class there is an excellent correlation between its calculated part of serum Ig synthesis and its part of Ig containing bone marrow cells Furthermore there is a high correlation between the serum concentration of each Ig class and the number of bone marrow cells positive for that class expressed as ‰ of the total cell population It may be concluded that changes in synthetic rate and serum concentration of the three major Ig classes are equalled by parallel changes in the Ig containing bone marrow cell

Table IV *Frequency of Ig containing cells total cellularity and total number of Ig positive cells in bone marrow spleen and lymph nodes*

	Positive cells ( )	Total cell popu lat on	Total Ig positive cell popu lation
Bone marrow	15 3	15×10 ¹	2 3×10 ⁰
Spleens	5 9[b]	8×10 [ac]	4 7×10[a]
Lymph nodes	0 7[b]	14×10	9 8×10[a]

[a] Corrected for normal serum Ig concentrations
[b] Positive cells/1 000 lymphoid cells after correlat on for a lymphoid cell concentration of 75% (spleens) and 90% (lymph nodes)
[c] Lymphoid cell population

population A high positive correlation between the total number of Ig-containing bone marrow cells and the total body pool of Ig was also reported by Vossen (58) in children

The cell profile in the tonsils is rather similar to that in the bone marrow but the distribution pattern in the lymph nodes and the spleens is different These organs contain considerably less α positive and the lymp nodes more μ and γ positive cells than would be the case if the cellular distribution by Ig classes corresponded to that of serum Ig syn thesis The number of IgM and IgG positive cells is also higher than expected in the spleens although this difference is not statistically significant There is no significant correlation between the number of spleen lymph node or tonsil cells positive for one Ig class and the serum concentration or synthetic rate of that class

The Ig-containing cells of the bone marrow con stitute a much larger part of the total cell population than the cells in the spleen lymph nodes or tonsils This is true for all three Ig classes with one excep tion IgM-containing cells are as common in the spleen as in the bone marrow of patients with nor mal IgM levels If only the lymphoid cell population is considered the difference is still more pro nounced and exists also for IgM positive cells in the bone marrow versus spleen The total bone marrow nucleated cell population in a 70 kg man has been reported to be of the order of 15×10[11] cells (53) The number of lymphoid cells in an average spleen has been estimated to 0 8×10[11] (42) The total number of lymph node cells in man is more difficult to determine Hamilton (30) calculated the total number of lymphocytes to be 14×10[11] assuming 1% of the body weight to be lymphoid tissue Using these data and correcting for the lymphoid cell con tent of the spleen and lymph node preparations one can estimate the total number of Ig-containing cells in these organs (Table IV) It is evident that the major part of Ig-containing cells is found in the bone marrow The results are very similar to those re ported by McMillan et al (42) who studied in vitro IgG synthesis by human lymphoid tissues

Two well known sites of Ig production have not been included in the present study the peripheral blood and the lymphoid tissue of the digestive and respiratory tract Hijmans and Schuit (33) found that 49% of Ig-containing cells in peripheral blood were positive for IgA 23% for IgM and 28% for IgG a distribution pattern that is clearly different from the distribution of serum Ig synthesis A simi lar distribution was reported by Vossen in healthy adults (58) and by Sandberg Wollheim and Tures son in patients with multiple sclerosis (52) The frequency of positive cells was estimated to 1 5–2 0/1000 lymphoid cells (33) and the total number of peripheral blood lymphoid cells has been estimated to 2 6×10 ⁹ (42) which means that the Ig-containing cells of the peripheral blood consti tute only a minor part of all Ig producing cells Th[illegible] lymphoid tissue of the mucosal membranes is n[illegible] in Ig producing cells which are responsible f[illegible] local synthesis of immunoglobulins that are se[illegible] creted IgA is the dominant Ig in secretions wh[illegible] occurs as a dimer coupled to secretory compo[illegible] and IgA-positive cells outnumber cells co[illegible] other Ig classes (56)

Some observations in animals indica[illegible] mucosal Ig-producing cells might co[illegible] siderably to the serum IgA (57) A part of [illegible] exists as a dimer On the other han[illegible] serum IgA is compatible with a n[illegible] IgA system in the gut (37 51) and a [illegible] of the IgA positive bone marro[illegible] shown to contain dimeric IgA (4[illegible] regarding frequency of Ig-co[illegible] that the bulk of serum IgA [illegible] marrow cells and that the [illegible] cretory system is of minor [illegible]

The da[illegible] presented her[illegible] relation to what is know[illegible] cell kinetics in mamm[illegible] has been a matter of [illegible] the century but e[illegible] are descendants of [illegible] the bone marrow [illegible]

upon antigenic stimulation proliferate and trans form into cells producing specific antibody Using autoradiographic techniques plasmacytopoiesis has been demonstrated in the popliteal lymph node of rats following antigenic stimulation (48) The cel lular reactions within the node are also reflected in the efferent lymph After an antigenic challenge the output of cells in the efferent lymphatic of the sheep popliteal lymph node is first arrested and then greatly increased (26) Large basophilic cells appear and many of these contain antibody (27) At the peak of the response up to 40% of the cells in the efferent lymph may be blast cells and of these two thirds may contain specific antibody (31) Cells with the ultrastructural characteristics of mature plasma cells are not released into the efferent lymphatic although they may be abundant within the node and still be present there after the immune response in the lymph has died away (46)

The ultimate fate of the antibody producing cells in the efferent lymph is not known in detail Some of them develop into mature antibody secreting plasma cells (28) Others may give rise to memory cells with the morphological characteristics of small lymphocytes (6) They have been demonstrated in the thoracic duct lymph in a more generalized antigenic stimulation (47) and seem to be important for the dissemination of the immune response since no general immunity develops if the efferent lymph from an antigenically stimulated lymph node is pre vented from reaching the blood stream (54) Only a small minority reenter the lymph after gaining the blood stream (53) A large proportion of them home to the lamina propria of the small gut (24 29) Oth ers very likely colonize the bone marrow It is known that the bone marrow is incapable of anti body synthesis in a primary immune response but takes part in a secondary response (6 40) It has also been demonstrated that memory cells appear in the bone marrow of mice after antigenic stimula tion so that a subsequent dose of antigen triggers the development of B memory cells into plaque forming cells (5 6)

These data are compatible with the hypothesis that in man the function of peripheral lymphoid organs in maintaining humoral immunity is mainly to provide optimal conditions for starting and dis seminating an immune response while the bulk of serum immunoglobulins are produced in the bone marrow as a result of repeated secondary antigenic stimulation

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Interstitial Nephritis with Acute Renal Failure Following Cardiac Surgery and Treatment with Methicillin

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ABSTRACT Six patients developed acute renal failure 13–19 days after cardiac surgery with extracorporeal circulation None of the patients had suffered from postoperative hypotension slight hemolysis was present for only 1–2 days postoperatively Acute renal failure lasted for 11–80 days in four patients In two patients creatinine clearance stabilized at reduced values Seven renal biopsies from the six patients showed severe acute interstitial nephritis with mononuclear cellular infiltration and distal tubular damage No immune deposits were detected in glomeruli or tubular basement membrane All six patients had been treated prophylactically with methicillin and the acute renal disease was probably elicited by this drug

This is a report of the clinical observations and the histological lesions in seven renal biopsies from six patients who were transferred to our department during the period Nov 1972–Oct 1974 with acute renal failure following cardiac surgery None of the patients had suffered from postoperative hypotension Hemolysis was present for only 1–2 days postoperatively and did not exceed that often seen in patients undergoing cardiac surgery All patients had been treated prophylactically with streptomycin and *methicillin They all showed a severe* acute interstitial nephritis in the biopsy specimens The clinical and histological data reported below support the presumption that the renal disease was elicited by methicillin

MATERIAL AND METHODS

Renal tissue obtained by percutaneous needle biopsy was fixed in Carnoy s fluid for histological studies Paraffin embedded tissue was cut into 2–3 μm thick sections and stained with hematoxylin-eosin van Gieson Hansen (for connective tissue) periodic acid Schiff hematoxylin phosphotungstic acid hematoxylin silver methenamine hematoxylin and by Giemsa s method

Immunofluorescence studies were carried out on cryostat sections from part of the biopsies Investigations for IgG IgA IgM IgD and IgE as well as complement (C_3) fibrinogen and albumin were performed as reported elsewhere (15)

RESULTS

Clinical observations The most pertinent clinical features in the six patients are summarized in Table I

All the patients underwent cardiac surgery involving extracorporeal circulation Five patients were operated upon for aortic stenosis with insertion of a Starr valve In one patient an artificial prothesis was inserted in order to correct an atrial septal defect of the primary type No complications occurred during the surgical procedure Extracorporeal perfusion lasted for 86–110 min BP was low during periods of perfusion although not below values ordinarily present under such circumstances No hypotensive periods were noted after operation Plasma Hb concentration was elevated during the first few days after operation with peak values between 10 and 36 mg/100 ml Also in this respect the patients did not differ from those commonly seen after cardiac surgery with extracorporeal circulation and no hemolysis was detected at the onset of the renal failure or immediately before All patients were treated prophylactically with methicillin 2 g twice daily and streptomycin 1 g daily for 6–14 days

Febrile episodes occurred immediately after op

Table 1 *Most important clinical data from six patients with acute renal insufficiency following cardiac surgery*

d =days after operation Lucopenin®=methicillin Prostaphlin®=oxacillin

				Postoperative antibiotics				
Pat no	Sex	Age (y)	Diagnosis and operation	Drug	Start of treatment (d)	Duration (d)	Total dosage (g)	Biopsy (d)
1/110605	♂	67	Aortic stenosis Starr valve	Lucopenin	1	10	120	37
				Streptomycin	1	6	6	
				Prostaphlin	12	15	60	
				Sulphamethizole	26	6	36	
2/300122	♂	49	Aortic stenosis Starr valve	Lucopenin	1	14	168	22
				Streptomycin	1	7	7	
				Prostaphlin	10	7	28	
3/140613	♂	60	Aortic stenosis Starr valve	Lucopenin	1	14	168	35
				Streptomycin	1	10	10	
				Garamycin	19	17	2 04	
				Keflin	19	17	102	
				Nitrofurantoin	17	3	1 2	
4/191101	♂	71	Aortic stenosis Starr valve	Lucopenin	1	8	96	21
				Streptomycin	1	6	6	55
5/200342	♀	32	Atrial septal defect Surgical closure	Lucopenin	1	11	132	36
				Streptomycin	1	7	7	
				Nitrofurantoin	9	4	1 6	
				Prostaphlin	13	10	40	
6/291012	♂	62	Aortic stenosis Starr valve	Lucopenin	1	12	102	48
				Streptomycin	1	8	8	
				Sulphamethizole	15	2	4	

* Defined as duration of azotemia urinary volume <500 ml/day

eration and often with secondary peaks 11–15 days er Multiple blood cultures were all negative and infective foci were found particularly no signs or symptoms of urinary infection were detected Leukocyte and differential counts performed during the renal failure in five patients revealed eosinophilia (11% and 15% of total leukocyte count) in two of them (nos 3 and 5)

Preoperative renal function (evalulated from serum creatinine concentration) was normal in all All patients developed acute renal failure 13–19 days after operation Patients 2 4 and 6 who were anuric for 5–19 days were treated with hemodialysis Patients 1 3 and 5 showed reduced renal function with minimum creatinine clearance at 11 15 and 25 ml/min respectively Renal failure lasted for 11–80 days in four patients two still have reduced renal function 48 and 319 days respectively after the onset of the disease

Proteinuria with urinary protein excretions of 0 2–2 4 g/day occurred during renal failure in five patients The proteinuria disappeared on normalization of renal function Slight intermittent hematuria and leukocyturia were noted in all patients

Pathology Seven renal biopsies from the six patients were studied by *light microscopy* The histology was almost identical in all specimens (Figs 1–3)

The most impressive lesion was a patchy but severe infiltration with mononuclear cells Small or large lymphocytes predominated but a variable number of larger cells which had the appearance of histiocytes were also present They had medium sized round or slightly indented nuclei surrounded by abundant clear cytoplasm Interstitial edema was often present in some areas Very thin collagen fibrils often surrounded single cells or groups of lymphocytes and histiocytes Scattered foci of histiocytes had at times the appearance of small granulomas Plasma cells were nearly always pres

Renal failure			
Appearance (d)	Duration (d)	No of hemodialyses	Outcome
13	80	0	Recovery
7	52	2	Recovery
18	31	0	Recovery
15	–	10	Serum creatinine 1 9 mg/100 ml 319 d postoperatively
19	11	0	Recovery
14	–	7	Serum creatinine 3 2 mg/100 ml 48 d postoperatively

ent but comprised only a small percentage of the cellular population Neutrophils and eosinophils occurred only rarely

The proximal tubules were nearly all normal Distal tubules were often degenerated with atrophy or swelling of the tubular epithelium Distal epithelial *necroses with disintegration of the cytoplasm and* nuclear pyknosis or rhexis were frequent In other tubules the epithelial cells were dark and low as in regeneration with many mitoses Distal tubular epithelium was often shed with presence of whole cells or cellular detritus in the lumina and with partly or totally denuded basement membrane Most of the tubular profiles situated in the densest interstitial cellular infiltrates showed diminished stainability of the tubular basement membranes and the whole basement membrane could be lacking In such cases small groups of degenerated tubular epithelial cells were situated between mononuclear cells in the interstitium When the tubular degeneration was most pronounced it was impossible to identify the part of the nephron which was represented but all transitions from well preserved distal tubules to the most severe tubular damage were seen Where the cellular infiltrates were less intense several normal groups of proximal tubules were present Tubular dilatation was *not* a characteristic feature and tubular casts were rare On morphometrical measurements normal values for the size of proximal tubular lumina were obtained whereas the mean size of distal tubular lumina was slightly augmented The interstitial volume was much distended making up more than 50% of the total renal cortical volume Compared with biopsies from patients suffering *from acute renal failure following shock hemolysis* etc the present cases differed significantly in several of the histological and morphometrical lesions described above (*14*)

Arteries and arterioles were normal or showed slight or moderate thickening of the walls Dilated capillaries and venules were often seen some of them containing lymphocytes The venules often showed rupture of the wall and small accumulations of fibrin could be present in the interstitium near the vessel Tubulo venous anastomoses or aneurysms were not identified

Glomeruli were always normal with the exception of a few which were hyaline sclerotic The medulla was normal or showed some interstitial fibrosis but did not contain mononuclear cellular infiltrates

The *immunofluorescent study* did not disclose any deposits in glomeruli or tubular basement membranes

DISCUSSION

The severe interstitial inflammatory infiltration *which was one of the most impressive lesions in our* cases suggests that the renal lesions seen in our patients belong to the group of so-called interstitial nephritides This lesion was originally described by Councilman in 1898 (6) Whereas some authors are reluctant to see any reason for this classification (11) because it conveys the false idea of a specific disease entity others have regarded the concept as useful (5 19)

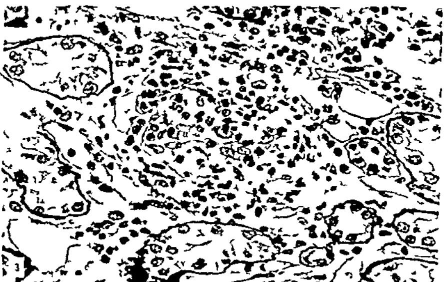
Zollinger and his coworkers have analysed cases of acute interstitial nephritis in several papers (19) They identified the lesion in diseases of varying etiology acute renal insufficiency with chromoproteinuria in cases of hemolysis or myolysis



Fg 1 K dney b opsy 37 days postoperat vely from patient 1 (serum creat n ne 4 3 mg/100 ml) Patchy nterst t al inf ltrat on with mononuclear cells (S lver methenam ne hematoxyl n)



Fg 2 Normal glomerulus surrounded by a heavy n terst t al inf ltrat on w th mononuclear cells Same biopsy and sta n ng as in Fg 1



Fg 3 Focus of severe mononuclear nf ltrat on w th remnants of d stal tu bul The basement mem branes are fa ntly sta ned or absent The ep thel al cells are necrot c or degenerated Around this focus tubular prof les show s gns of regen erat on (m tos s) Same b opsy and sta n ng as n Fg 1

leptospirosis burns and severe infection They were aware of the similarity of this renal lesion to that seen in acute interstitial renal allograft rejec tion Zollinger insisted on the non-destructive character of the inflammation with only very slight tubular damage In contrast all our specimens showed severe d stal tubular damage with dis appearance of the tubular basement membranes and disrupture as well as necrosis of the tubular epi thel um

All our patients had undergone cardiac surgery 13–19 days before the onset of the renal failure This raises the question of a causal relationship Yeboah et al (18) investigated the occurrence of acute renal failure following open heart surgery in a series of 429 patients They found that 26% had mild renal failure Only 4 7% had severe renal failure and only 19 of 40 autopsied patients who died in renal failure showed renal lesions at autopsy These consisted of acute tubular necrosis infarctions and pyemic abscesses Interstitial nephritis was not present in any of their patients Our patients did not show any signs of chromoproteinuria as described by Zollinger and the severity and duration of hemolysis following operation in our patients did not exceed that seen after cardiac surgery in general Moreover renal failure developed several days after the operations Hence it seems unlikely that renal insufficiency in our patients was due to hemolysis Small emboli have been thought to be able to provoke interstitial nephritis Vascular occlusions or microinfarcts were however not noted in our biopsies Hypotension or shock had not been present in any of our patients

During the period in which our cases were observed all patients in the Department of Cardiac Surgery at this hospital were treated with several antibiotics and chemotherapeutics during the postoperative period Common for all patients reported was prophylatic treatment with Lucopenin (methicillin) and streptomycin from the day of the operation until the 6th or 14th day Both of these drugs are known to be nephrotoxic in some patients Renal complications caused by streptomycin are rare events and histologically they are characterized by proximal tubular damage (1) or glomerular lesions (10) without severe interstitial inflammation

Penicillins and specifically methicillin have been shown to be nephrotoxic (2 3 4 7 8 9 12 13 16 17) The nephropathy presents in some cases clinically as acute renal failure Histologically it is characterized by acute interstitial infiltration with mononuclear cells as well as severe distal tubular damage identical with that observed in our patients We regard it therefore as highly probable that the acute renal failure in our patients was elicited by methicillin although it remains a possibility that streptomycin may have had an additive effect

It should perhaps be emphasized that in earlier reports of renal disease thought to be due to methicillin the possibility could not be ruled out that infection was the causative factor and not the drug All our patients however were treated *prophylactically* and no underlying infection was found

The pathogenesis of methicillin nephropathy is not known A direct toxicity seems less probable because the renal damage develops in only a small percentage of patients receiving this drug and no evident dependency of dosage has been demonstrated Since many reported cases have been characterized by fever skin rash and sometimes eosinophilia an allergic mechanism could be operative The time lag which is often present between the start of methicillin treatment and the onset of renal symptoms also speaks in favour of this assumption Baldwin et al (2) using an immunofluorescence technique were able to identify penicilloyl hapten and γ-globulin in glomerular and tubular basement membranes in one patient suffering from methicillin induced renal failure Recently Border et al (3) reported on a patient in whom IgG C_3 and penicilloyl hapten were demonstrated along the tubular basement membranes These observations were interpreted as indicating a coupling of the hapten to the proteins of the tubular basement membranes As a consequence antitubular antibodies (which were in fact demonstrated in the serum of the patient of Border et al) could be responsible for the tubular lesions and the interstitial inflammation might then be secondary to the tubular damage

None of our patients showed immunoglobulin deposits in the tubular basement membranes although we have been able to demonstrate such deposits in another patient with methicillin induced interstitial nephritis not occurring after cardiac surgery and therefore not included in this report However lesions of distal tubules as well as of their basement membranes were prominent While it remains uncertain what kind of lesion was responsible for the tubular lesions in our cases it could hypothetically be proposed that an initial lesion of the tubular epithelial cells and/or the basement membranes subsequently resulted in a cellular immunoreaction against abnormal proteins in the tubules or their basement membranes The dense infiltrates consisting of small and large lymphocytes occurring preferably around abnormal tubules could afford some evidence for this mechanism Further studies are clearly needed to solve the pathogenetic problems of methicillin induced renal disease

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The Urinary Excretion of Ten plasma proteins in Long-term Renal Transplant Patients

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ABSTRACT Using an automated immunoprecipitin reaction, the urinary excretion of albumin, transferrin haptoglobin, IgM, IgG, IgA, free lambda and kappa light chains from immunoglobulin, lysozyme and β_2-microglobulin has been investigated in 40 long term bilaterally nephrectomized renal transplant patients The excretion of the proteins, except lysozyme, was significantly increased in 21 of the patients with Albustix® negative urine In patients with glomerulonephritis prior to the transplantation, the excretion of albumin, transferrin and IgG was significantly increased compared with the other patients The IgM excretion was significantly increased in patients who had received C and D matches compared with those with A and B matches Patients with severe surgical complications in the postoperative period had a tubular proteinuria and in patients surviving more than 60 months after transplantation the excretion of several proteins was significantly increased *compared with patients surviving less than 60* months

Determination of protein patterns and specific proteins in urine by means of electrophoresis and immunochemical methods provides more information about the character of proteinuria and often about the nature of the kidney disease than determination of the total protein excretion (2 19 25 26)

The aim of the present investigation was to examine whether the determination of 10 specific proteins in the urine provides more exact information about a transplanted kidney than the determination of total urinary protein especially when the total protein excretion is within the empiric normal range (10) We also examined the contribution of different factors to the excretion of the proteins i e primary kidney disease match grade duration of the warm and cold periods of ischaemia number of earlier rejections surgical complications interval between renal transplantation and investigation and renal function at the time of evaluation

Finally the investigation serves as a basis for a follow up study of long term renal transplant patients particularly concerning the early diagnosis of a chronic rejection or a late acute rejection

The proteins examined were six of high molecular weight albumin transferrin haptoglobin IgM IgG and IgA and four of low molecular weight free lambda and kappa light chains from immunoglobulin lysozyme and β_2 microglobulin The determinations of these proteins should be considered as protein related material because some or all of the proteins may be present in the urine also as split products with preserved antigenic determinants

MATERIAL AND METHODS

The material consisted of 40 consecutive bilaterally nephrectomized transplant recipients 19 women and 21 men aged 22–60 years and 221 adult control subjects (11) The patients had received kidney transplants during 1968–74 Thirty two patients had primary grafts 8 secondary the first graft had been removed in 6 patients

In Table I which lists some characteristics of the patients the material is divided into three groups according to the degree of proteinuria The patients in group I had a total protein excretion within the normal range (<300 mg/24 h) and the urine was Albustix® negative The patients in group II had a protein excretion of 300–3 500 mg/24 h and those in group III had a nephrotic type of proteinuria (≥3 500 mg/24 h)

The interval between transplantation and evaluation did not differ between the three groups and averaged 45 7 months

The incidence of glomerulonephritis prior to transplan

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Table I *Characteristics of 40 long term renal transplant patients*

	Degree of proteinuria (mg/24 h)	No of pats	Interval between transplantation and evaluation (mo)[a]	Preceding glomerulonephritis (%)	(n)	Rejection frequency[b]	Serum creatinine[c] (μmol/l)	Creatinine clearance[c] (ml/min/1 73 m²)
Group I	<300	21	47 7 (6–77)	24	5	0 67	107 (59–137)	66 (50–105)
Group II	≥300<3 500	13	41 7 (5–65)	77	10	0 77	136 (75–209)	68 (31–104)
Group III	>3 500	6	47 7 (16–72)	50	3	1 00	292 (113–564)	21 (10–56)

[a] Average and range   [b] Total no of rejections/no of patients   [c] Median and range

tation was 24% in group I 77% in group II and 50% in group III thus significantly higher in group II than in group I ($p<0\ 01$) no significant difference was found between group III and the other groups The remaining patients suffered from chronic pyelonephritis polycystic kidneys malignant hypertension and various malformations of the urinary tract The primary disease was diagnosed from the clinical history and from histological examination of the original kidneys compared with histological examination of any renal biopsy prior to the nephrectomy

The rejection frequency (total no of rejections/no of patients) was 0 67 0 77 and 1 00 in groups I II and III respectively These differences were not significant

Eight patients received A–B matches and 32 C–D matches Nine patients received transplants from living related donors and 31 received necrokidneys Twenty two patients had a period of warm ischaemia ≤10 min and 17 patients >10 min Thirty-one patients had a period of cold ischaemia <600 min and 8 patients ≥600 min In one tient the periods of ischaemia were unknown

The transplantation technic employed was similar in all The postoperative immunosuppressive regime consisted of azathioprine and prednisone When acute rejection crises were diagnosed the prednisone dosage was increased or treatment with methylprednisolone was started (17) No patients were treated with antilymphocyte agents

Severe surgical complications occurred in 9 patients during the first three postoperative weeks The surgical complications included severe uroplania and ureterovesical stenosis requiring reoperation or severe bleeding episodes with large perigraft haematomas requiring reoperation Complications involving the renal artery or vein were not encountered

From Oct 1974 to Jan 1975 24 hour urines were collected venous blood was drawn and the history of the patients examined

The analysis of urinary and serum proteins was carried out on AutoAnalyzer® (Technicon Corp Terrytown N Y) for determination of specific proteins The method used was an automated immunoprecipitin reaction The precipitate was measured by means of a fluoronephelometer In order to increase the sensitivity the standard method was modified as described previously (11) The average sensitivity was 0 1 mg/l depending on the range of measurement The precision of the apparatus and the method as stated by the coefficient of variation was for all components of protein on an average 4 6% and 9 6% respectively The analytical capacity was 60 specimens/hour

The urinary and serum creatinine concentrations were determined by Jaffes reaction (AutoAnalyzer®) The urinary sediment was examined for erythrocytes leucocytes casts bacteria and the urine was cultivated for bacteria

The clearances of the six high molecular weight proteins were calculated according to Ravnskov (23) by means of the formula

$$\frac{U_P\ V/S_P}{U_{Cr}\ V/S_{Cr}}$$

where U_P and S_P denote the urinary and serum concentration of the specific protein U_{Cr} and S_{Cr} the urinary and serum concentration of creatinine and V urine volume/unit of time

The non parametric Wilcoxon test was employed for evaluation of the protein excretion and the protein clearances As significant we consider $p<0\ 01$ as possibly significant $p>0\ 01<0\ 05$ and as insignificant $p\geq0\ 05$ The distribution of preceding disease match ischaemia rejection surgical complication interval and renal function in the groups in question was tested by means of the χ^2 test

RESULTS

The 24 hour urinary excretion of the 10 specific proteins is shown in Table II Table III lists the clearances of the six high molecular weight proteins Comparing all patients with the controls the 24 hour excretion and the clearance of all proteins except lysozyme were significantly increased in the patients The same result was obtained when group I was compared with the control subjects However the concentration of serum creatinine

Table II *Urinary protein excretion (mg/24 h) in 40 long term renal transplant patients and 221 controls (median and range)*

	Controls	Patients: Total	Group I	Group II	Group III
Albumin	6 2 (1 6–34 2)	64* (6–9 027)	15 2 * (6 4–98 3)	191 (34–801)	5 175 * (4 290–9 027)
Transferrin	0 68 (0 00–3 50)	8 2** (0–840)	2 23 (0 0–9 9)	26 0 * (2 9–58 0)	400 * (262–840)
Haptoglobin	0 10 (0 00–0 95)	1 3 * (0–647)	0 60 * (0 0–2 1)	2 08 (0 2 15 4)	21 9 (1 8–647)
IgM	0 34 (0 00–1 34)	1 9 * (0 0–9 7)	1 75 (0 0–9 7)	2 48 (0 0–4 9)	2 00 (0 0–5 3)
IgG	1 93 (0 20–6 50)	8 1* (0–646)	2 57 (0 0–28 0)	13 4 (2 4–47 6)	185 (108–646)
IgA	0 58 (0 00–2 25)	2 6** (0–240)	1 50 (0 0–7 6)	3 77* (0 9–19 0)	45 1 (35–240)
Lambda	1 40 (0 00–7 60)	6 9** (0–244)	3 22 * (0 0–28 3)	8 91 (3 0–56 1)	82 4 * (22 244)
Kappa	2 30 (0 00–9 00)	9 3* (1 3–193)	3 33 (1 3–78 1)	16 6 (3 7–83 5)	86 4 * (46–193)
Lysozyme	0 16 (0 02–0 45)	0 16 (0 0–1 0)	0 09 (0 00–0 55)	0 16 (0 05–0 86)	0 32** (0 22 1 00)
β_2 microglobulin	0 04 (0 00–0 14)	0 25** (0 0–10 2)	0 09 (0 00–0 68)	0 31* (0 00–7 38)	3 28* (0 72 10 20)

All patients versus controls **$p<0\ 01$ Group I versus controls **$p<0\ 01$ Group II versus group I * $p<0\ 01$
Group III versus group I **$p<0\ 01$

was significantly increased and the creatinine clearance significantly decreased in group I compared with the controls Therefore group I was revised excluding the patients with impaired renal function Only the patients ($n=13$) with normal serum creatinine concentration and normal creatinine clearance related to body surface age and sex (16) were compared with the control subjects The result was almost similar to that of group I only the excretion of the free λ light chains was not significantly increased

Finally group II and group III were compared with group I In groups II and III the 24 hour excretion and the clearance of albumin transferrin

Table III *Protein clearance related to creatinine clearance (1×10^{6}) in 40 long term renal transplant patients and 221 controls (median and range)*

	Controls	Patients: Total	Group I	Group II	Group III
Albumin	1 0 (0 4–6 3)	16 * (1 26 130)	3 3* (1–40)	58* (6–206)	6 355 (1 434– 6 130)
Transferrin	1 6 (0 0–7 0)	28 * (0–21 790)	6 0 (0–42)	84 * (7 204)	4 844 (1 082–21 790)
Haptoglobin	0 8 (0 0–5 2)	12 * (0–11 850)	4 0 (0–16)	14 (1–87)	288 (75–11 850)
IgM	1 8 (0 0–15 1)	15* (0–198)	9 5 (0–198)	18 (0–158)	82 (0–156)
IgG	1 2 (0 3–4 6)	10 (0–12 190)	3 2 (0–35)	20 (5–130)	1 588 (284–12 190)
IgA	1 7 (0 0–7 0)	17* (0–7 456)	6 5* (0–135)	24 * (6–110)	2 096** (390–7 456)

All patients versus controls $p<0\ 01$ Group I versus controls $p<0\ 01$ Group II versus group I $p<0\ 01$
Group III versus group I * $p<0\ 01$

Table IV *Protein excretion (mg/24 h) in long term renal transplant patients related to the preceding disease*

	Glomerulonephritis (n≈18)		*Other than glomerulonephritis* (n=22)	
	Median	Range	Median	Range
Albumin	269**	9 0–9 027	27 9	6 4–7 059
Transferrin	21 5*	0 0–840	3 43	0 0–762
Haptoglobin	1 83	0 0–647	0 88	0 1–26 9
IgM	1 85	0 0–5 3	1 95	0 0–9 7
IgG	12 1*	1 6–646	5 85	0 0–373
IgA	2 81	0 0–240	2 36	0 0–61 0
Lambda	8 89	0 7–244	3 80	0 0–143
Kappa	14 6	1 9–193	5 66	1 3–162
Lysozyme	0 16	0 0–1 0	0 15	0 0–0 6
β_2 microglobulin	0 27	0 0–8 6	0 12	0 0–10 2

** p<0 01 p<0 05

haptoglobin IgG and IgA were significantly increased the IgM excretion was unchanged In group II the excretion of the free λ and κ light chains and β_2 microglobulin was significantly increased and in group III the excretion of all four low molecular weight proteins was significantly increased

Table IV shows that the excretion of 9 out of 10 specific proteins was increased in the patients who had suffered from glomerulonephritis prior to the transplantation compared with the patients with receding disease other than glomerulonephritis e increased excretion of albumin was significant ile the increased excretion of transferrin and IgG was possibly significant There were no differences in the distribution of the remaining factors

Table V *Protein excretion (mg/24 h) in long term renal transplant patients related to the incidence of major surgical complications*

	Pats with major surgical complications (n=9)		Pats without major surgical complications (n=31)	
	Median	Range	Median	Range
Lambda	11 1	0 8–143	6 09	0 0–244
Kappa	11 2	3 0–162	8 53	1 3–193
Lysozyme	0 38*	0 0–0 9	0 15	0 0–1 0
β_2 microglobulin	0 32	0 0–10 2	0 17	0 0–8 6

* p<0 05

Table VI *Protein excretion (mg/24 h) in long term renal transplant patients related to the interval between transplantation and evaluation*

	5–59 months (n=30)		≥60 months (n=10)	
	Median	Range	Median	Range
Albumin	52 9	6 4–7 059	262	9 0–9 027
Transferrin	5 90	0 0–762	22 3	0 0–840
Haptoglobin	0 88	0 1–40 0	1 87	0 0–647
IgM	1 71	0 0–9 7	2 00	0 0–5 9
IgG	6 42	0 0–373	13 6*	1 0–646
IgA	2 16	0 0–61 0	5 44**	1 5–240
Lambda	3 44	0 0–143	17 8**	4 2–244
Kappa	6 26	1 3–162	23 9*	3 2–193
Lysozyme	0 14	0 0–0 9	0 22*	0 1–1 0
β_2 microglobulin	0 15	0 0–10 2	0 33*	0 1–8 6

**p<0 01 *p<0 05

The IgM excretion in patients with transplants of C and D match grades was significantly increased 2 33 mg/24 h (0 00–9 69) compared with patients with A and B matches 0 72 mg/24 h (0 00–1 73) The excretion of the other proteins examined was identical in the two groups Patients with A and B matches had less frequent rejection episodes than those with C and D matches The two groups did not differ concerning the distribution of the remaining factors

The urinary excretion of the proteins was not influenced by the duration of either the warm or the cold period of ischaemia

In patients with one or more rejection episodes the excretion of all the proteins examined was increased compared with patients without rejection episodes but not significantly

Table V shows that the excretion of the four low molecular weight proteins was increased in patients with severe surgical complications compared with patients without such complications The two groups did not differ concerning the excretion of the six high molecular weight proteins and the distribution of the remaining factors

Table VI shows that the excretion of the 10 plasma proteins examined was increased in patients surviving more than 60 months (average 67 5) compared with those surviving less than 60 months (average 38 5) after renal transplantation The excretion of IgA and free λ light chains was significantly increased The two groups did not differ concerning the distribution of the remaining factors

In patients with a creatinine clearance <70 ml/min the excretion of all the proteins examined was increased compared with patients with a creatinine clearance ≥70 ml/min but not significantly

DISCUSSION

The excretion of 9 out of 10 plasma proteins was significantly increased in the urine from 40 long term bilaterally nephrectomized transplant recipients An identical result was found in 21 of these patients who had a nearly normal clearance normal BP Albustix® negative urine and a normal total urine protein excretion (group I) Concerning the excretion of the four low molecular weight proteins Revillard et al (24) point out that tubular proteinuria appears as a constant feature in transplanted patients with normal clinical course However as regards the high molecular weight proteins this finding has not been published earlier and it demonstrates that the determination of these proteins gives more information about the state of the graft than does measurement of total urinary protein

Thus our results imply glomerular injury in apparently well functioning long term renal transplants Only in three patients was the excretion of all ten proteins within the normal limits This is in agreement with the results of histological examinations including light and electron microscopy as well as immunofluorescence microscopy of biopsies from transplanted patients fulfilling the same criteria as the patients in group I in the present study No normal biopsies were demonstrated in the series of Fisch et al (4) Glassock et al (6) and Porter et al (22) Normal biopsies concerning the glomeruli were however found more frequently in later studies (13 14)

The nature of this glomerular lesion in transplanted kidneys has been somewhat disputed Some investigators hold that it is caused by a de novo glomerulopathy which develops on account of histoincompatibility (7 18 22) whereas others are of the opinion that an original glomerulonephritis is transmitted to the graft (1 3 5 8 12 15)

In our study only 5 patients in group I had glomerulonephritis as the original disease Thus the glomerular lesion in the other 16 patients of the group could not be caused by transmission of glomerulonephritis to the graft

In groups II and III ($n=19$) a more severe glomerular injury was encountered as demonstrated by a heavier proteinuria and a decreased creatinine clearance Of these patients 13 had glomerulonephritis as the primary kidney disease Thus in these groups the transplant glomerular disease may have been caused by transmission of glomerulonephritis in 68% of the cases As the time of observation was identical in the three groups this finding may indicate a worse prognosis in glomerular transplant disease caused by transmission of glomerulonephritis than caused by a de novo glomerulopathy However only further studies can decide whether this assumption is correct

The considerably increased excretion of the 10 plasma proteins in patients surviving more than 5 years after renal transplantation (Table VI) demonstrates that all long term transplanted kidneys develop a pronounced transplant glomerular disease independent of the different pathogenetic mechanisms involved

The significantly increased total protein excretion in patients with poor match grades and several rejection episodes demonstrated in previous investigations (9 27) was not found in the present study However the significantly increased IgM excretion found in our patients with poor match grades has not been demonstrated before

The duration of the periods of ischaemia did not influence the protein excretion significantly As the periods of ischaemia were never extremely long this result is in accordance with findings in autografts in which the pathological changes caused by the ischaemia frequently disappeared within a few months (21)

Tubular proteinuria after urinary obstruction (19 20) persisted in the present study months to years after correction of the surgical complications in question

In conclusion the results of the study demonstrate 1) Determination of specific proteins supplies more information than does measurement of total urinary protein 2) Glomerular transplant disease exists in almost all grafts This disease may be caused by transmission of a primary glomerulonephritis as well as by a de novo glomerulopathy the prognosis for the graft possibly being better in de novo glomerulopathy 3) Poor match grades result in an increased urinary excretion of IgM 4) Persistence of tubular proteinuria months to after corrected surgical complications

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The Effect on Serum Enzymes of Intramuscular Injections of Digoxin, Bumetanide, Pentazocine and Isotonic Sodium Chloride

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ABSTRACT Intramuscular injections of digoxin, bumetanide, pentazocine or isotonic sodium chloride have been given to 39 patients We followed the serum concentrations of creatine kinase (CK) aspartate aminotransferase (ASAT), lactate dehydrogenase (LDH) and LDH isoenzymes for 4 days Ten patients receiving 500 µg digoxin showed a significant rise in CK, which lasted for 48 hours, and 6 of them had CK values exceeding the upper normal limit Pentazocine in a dose of 30 mg given to 9 patients caused a significant rise in CK and LDH isoenzyme 1, but in no case did the level exceed the upper normal limit No rise in ASAT or total LDH was found after digoxin and pentazocine injections No changes in enzymes were discovered after bumetanide or isotonic sodium chloride In the diagnostic evaluation of acute myocardial infarction a moderate rise in CK must be assessed with caution when the patients have received i m injections of drugs with osmolarity and pH outside the physiological limits

If patients with suspected myocardial infarction are treated with drugs given intramuscularly diagnostic difficulties may occur if such injections give rise to serum enzyme values

MATERIAL AND METHODS

A total of 39 in patients were studied with their informed consent Most of them had recovered from an acute myocardial infarction (AMI) and none were in need of i m injections None of the patients had active infection liver disease cancer or muscular dystrophy The patients were sedentary apart from the mobilization programme The selection of patients was determined by two successive normal enzymes and not at random All the i m injections were given by the same nurse deep in the lateral gluteal region and always at the same time of day (9 a m) In the case of sodium chloride three injections were given on the same day at 9 and 11 a m and 1 p m

Ten patients received 500 µg digoxin (Wellcome) in 2 0 ml solution containing 10% ethanol 96% and 40% propylenglycol equivalent to 246 02 g sodium chloride per litre thus strongly hypertonic Nine patients received 30 mg pentazocine (Winthrop) in 1 0 ml isotonic solution with a pH of 4 7–4 8 Ten patients had injections of 1 mg bumetanide (Leo) in 4 ml isotonic solution with a pH of 7 4 and ten patients received 6 ml isotonic sodium chloride None of the patients in the digoxin group were on digitalis medication and the serum potassium was within normal limits

Blood specimens were taken on the day before the examination immediately before the injection 7 hours later at 4 p m and on the next three days (Figs 1 and 2) The enzymes were analysed on an LKB 8600 Reaction Rate Analyzer using the kinetic method with Baker s Utilizers at 37°C within 24 hours (5 6) The upper normal limit for CK in our laboratory is 170 U/l for men and 100 U/l for women The variation coefficient is less than 4 9%

Statistics

The Friedman two-way analysis of variance was used and the 1% significance level was adopted When a significant difference is found a parametric analysis of variance is employed for multiple comparisons

RESULTS

Fig 1 shows the CK level (U/l) in the digoxin group before and after the injection

Statistical analysis indicates that the 6 mean values do not derive from the same population The values 7 24 and 48 hours after the injection are significantly elevated It should be noticed that in our material the elevation in CK after digoxin injection exceeds the upper normal limit in 6 of the 10 cases with a maximum twice the upper normal limit

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Lysozyme Activity in Cerebrospinal Fluid

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ABSTRACT The concentration of lysozyme (LZM) in cerebrospinal fluid (CSF) has been studied in 148 patients to evaluate its possible significance in the differential diagnosis of various diseases affecting the central nervous system (CNS) In the control group only 3 of 45 patients had detectable LZM in their CSF, the highest value being 1.3 μg/ml The diabetic and epileptic groups did not differ from the control group Of 8 patients with primary intracranial tumours, 4 had raised CSF LZM levels Twenty of 23 uraemic patients had elevated CSF LZM, the highest value being 3.3 μg/ml The highest values were found in patients with bacterial meningitis, tuberculous meningitis and leptomeningitis due to Aspergillus A positive correlation was found between CSF LZM and protein concentrations The measurement of LZM may be of value in the diagnosis of inflammatory processes affecting the CNS and in the diagnosis of certain intracranial tumours

Lysozyme (LZM) is a widely but selective distributed enzyme in man (4 8 11) High concentrations of LZM occur in phagocytic cells polymorphonuclear neutrophils (PMN) monocytes and macrophages as well as along the gastrointestinal tract and in the kidneys LZM has not been detected in cells of the central nervous system (CNS) (8) and normal cerebrospinal fluid (CSF) contains no LZM (4 5 6 17) However elevated CSF LZM levels have been recorded in bacterial meningitis (1 2 5 10 17) sarcoidosis of the CNS (10) and in certain CNS tumours (1 10 12)

This study was undertaken to study possible variations in the concentration of CSF LZM in a variety of disorders affecting the CNS

MATERIAL AND METHODS

The concentration of LZM in CSF was studied in 148 patients 45 with no evidence of toxic metabolic or local CNS disease (control group) 23 with non haemorrhagic thromboembolic cerebrovascular disease 24 with epilepsia 16 with manifest insulin-dependent diabetes 23 with various degrees of renal insufficiency 8 with intracranial tumours 7 with bacterial meningitis 1 with tuberculous meningitis and 1 with leptomeningitis caused by Aspergillus fumigatus

CSF was obtained by conventionally performed lumbar puncture Specimens were centrifuged at 2 000 rpm for 10 min and the supernatant was stored at −20°C until assayed Some cell free specimens of CSF were stored at +4 C for several weeks with no apparent effect on LZM activity Immediately after puncture the CSF was submitted to cell counts and protein determinations performed by routine methods

LZM was assayed by the lysoplate method described by Osserman and Lawlor in which purified human LZM is *used as standard (14) With the use of 10-μl micropipettes* (Eppendorf West-Germany) for filling the wells standardized gel thickness and 18 hour incubation at room temperature LZM activity was detected at enzyme concentrations of 0 9 μg/ml Values below this figure were considered to be zero The standard curve in Fig 1 shows the relationship between the concentration of human LZM (in concentrations of 1 10 μg/ml) and the diameter of the zone of lysis

The immunohistochemical identification of LZM in *CNS tumours was demonstrated by an immunoperoxidase* method as described previously (8)

RESULTS

Fig 2 gives the concentration of CSF LZM in a variety of CNS disorders

Control patients Of the 45 patients who had no evidence of any disease of the CNS 42 had no detectable (i e <0 9 μg/ml) LZM activity in their CSF In two patients the level was 0 9 μg/ml and in one 1 35 μg/ml

Non haemorrhagic thromboembolic cerebrovascular disease Thirteen of 23 patients had no demonstrable LZM activity in their CSF whereas ten had concentrations of CSF LZM ranging from 0 9 to 2 15 μg/ml

Epilepsia Seventeen of 24 patients with epilepsia

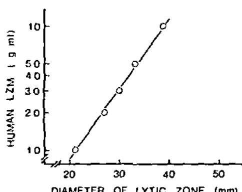


Fig 1 Lysoplate analysis of human LZM in concentrations of 1–10 μg/ml This method in which human LZM is used as standard gave reproducible results with concentrations of LZM in CSF above 0 9 μg/ml

had no detectable LZM activity In seven of them CSF LZM levels ranged from 0 9 to 1 35 μg/ml

Diabetes mellitus Some of the 16 patients with diabetes had diabetic complications such as diabetic retinopathy neuropathy and peripheral vascular insufficiency Fifteen of these 16 patients had no detectable LZM activity in their CSF in one the concentration of LZM was 0 9 μg/ml

Intracranial tumours We studied eight patients with primary neoplasms of the CNS (4 gliomas 1 astrocytoma 1 meningioma 2 hypophyseal adenomas) Four had no detectable LZM in their CSF and four had CSF LZM in concentrations of 1 5–2 4 μg/ml We stained three types of CNS tumours (2 meningiomas 2 gliomas 3 astrocytomas) with the immunoperoxidase method and could not detect LZM in any of these tumours

Renal disease Of the 23 patients in various stages of functional renal impairment (serum creatinine level >150 μmol/l) only three had CSF LZM concentrations below 0 9 μg/ml In 20 of these patients the concentration of LZM was between 0 9 and 3 3 μg/ml

Bacterial meningitis All seven patients with bacterial meningitis had raised levels of LZM in their CSF the lowest being 2 4 and the highest 24 0 μg/ml

In one patient with *tuberculous meningitis* and one with *leptomeningitis due to Aspergillus fumigatus* the concentration of LZM in the CSF was high (Table I)

We correlated the concentrations of CSF LZM with the following laboratory findings serum LZM levels CSF protein concentrations and serum creatinine levels In 35 patients there was no correlation between the concentration of LZM in serum and in CSF (Fig 3) The concentrations of LZM and protein in CSF correlated positively in the 23 uraemic patients ($r=0\ 622$ $p<0\ 01$) and in the eight

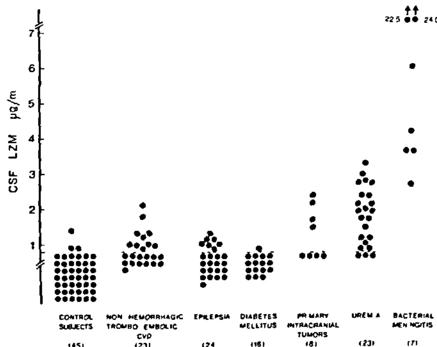


Fig 2 Concentrations of LZM in CSF in various disorders affecting the CNS

Table I *Data of the patient with tuberculous meningitis and the patient with cerebral aspergillosis*

MN=mononuclear cells PMN=polymorphonuclear cells ND=not done

	Sex	Age (y)	Duration of disease	Serum creatinine (μmol/l)	Serum LZM (μg/ml)	CSF LZM (μg/ml)	CSF protein (μg/ml)	CSF leukocytes (×10⁶/l)
Tuberculous meningitis	♀	77	1 mo	96	9 6	7 6	2 885	175 38 % PMN 62 % MN
Cerebral aspergillosis	♂	69	1 y	82	ND	3 7	1 480	100 1 % PMN 99 % MN

patients with intracranial tumours ($r=0\ 823$ $p<0\ 05$) In the seven patients with bacterial meningitis no positive correlation could be observed ($r=0\ 390$) (Fig 4) In the seven patients who had bacteriologically verified purulent meningitis LZM levels in CSF correlated neither with PMN counts nor with the species of bacteria involved In 23 patients with renal insufficiency as determined by serum creatinine levels the concentration of LZM in the CSF did not correlate with their uraemic state (Fig 5)

DISCUSSION

Our results agree with previous observations of LZM levels in normal CSF namely that these levels are extremely low (4 5 6 17) Moreover the CSF LZM levels in patients with diabetes mellitus and epilepsia did not differ from those in the control patients Our results also show that LZM levels are often elevated in patients with uraemia bacterial meningitis and tuberculous or fungal meningitis as well as in certain patients with intracranial tumours

The source of LZM in the CSF is clearly not the CNS tissue because LZM cannot be detected in these tissues not even in the choroid plexus by immunohistochemical staining techniques (8) To try to account for these results three possible origins of the LZM present in CSF can be considered namely a) that LZM reaches CSF by a simple diffusion process from serum b) that LZM is

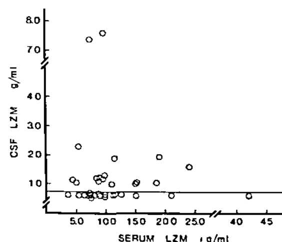


Fig 3 Results of simultaneous determinations of serum and CSF LZM levels in 35 patients No positive correlation

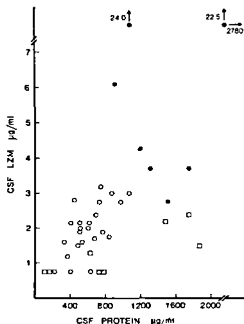


Fig 4 Results of correlations between the concentrations of LZM and protein in the CSF of patients with renal insufficiency (○) bacterial meningitis (●) and intracranial tumours (□) There was a positive correlation in the renal and tumour groups

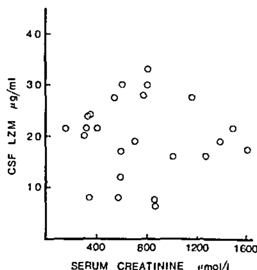


Fig 5 Correlation between the concentrations of CSF LZM and serum creatinine in 23 uraemic patients shows an absence of any positive correlation

derived from normal blood cells i e from neutrophilic granulocytes and monocytes or from free or fixed mononuclear phagocytes involved in an inflammatory process in the CNS and c) that LZM is derived from neoplastic cells of the CNS

The multiple and complex characteristics of the membranes that comprise the blood brain barrier in normal and pathological states are still poorly understood In uraemic patients barrier permeability seems to be affected which possibly results in a uraemic encephalopathy (3) In uraemic patients serum LZM levels are 5–8 times higher than normal reaching concentrations of about 30–40 μg/ml (13 16) Uraemic patients have an LZM/protein ratio in serum of about 1 2000 and in CSF of about 1 300 (Fig 4) This latter altered ratio probably reflects an enhanced diffusion through the blood brain barrier into CSF of such low molecular weight compounds as LZM (mol wt about 14 500) This diffusion of LZM into CSF was related to the amount of protein leakage into the CSF It can also be concluded that in uraemic patients there exists no definite threshold concentration of serum LZM that would trigger a rapid and passive diffusion of LZM into CSF This poor correlation between CSF and other serum enzyme elevations is in agreement with the findings of other investigators (7 9 18)

Of the 8 patients with intracranial CNS tumours 4 had slightly raised LZM levels in their CSF An elevation of CSF LZM levels has been attributed either to a malignant proliferation of an LZM producing cell type which occurs in histiocytic lymphomatous meningitis (12) or to a benign neoplastic proliferation of LZM containing monocytes or macrophages which occurs in granulomatous disease neurosyphilis and neurosarcoid (1 10) In the patients we studied none of the three types of tumours—meningiomas gliomas or astrocytomas—contained any LZM when biopsy specimens were stained for LZM with an immunoperoxidase technique Hence the LZM present in slight amounts in the CSF of these patients was either derived from inflammatory cells of the tumours or was present as a result of changes in the permeability of the blood brain barrier

Our observation of raised LZM levels in the CSF of patients with bacterial meningitis agrees with previous reports (1 2 5 10 17) Although the LZM concentration in the CSF of these patients did not correlate with the number of PMN this LZM probably originates from the inflammatory cells of the CSF In the patients with tuberculous meningitis and fungal leptomeningitis the case history of whom has been reported elsewhere (15) the most likely source of the high CSF LZM concentration was the mononuclear phagocytes present in the inflammatory granulomatous lesions The diagnostic value of LZM determinations in CSF appears to be limited to the diagnosis of inflammatory processes of the CNS including bacterial tuberculous or fungal infections whereas its diagnostic value in certain intracranial tumours needs further investigation

ACKNOWLEDGEMENTS

The study was supported by grants from the Finnish National Research Council for Medical Sciences and the Sigrid Jusélius Foundation

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BOOK REVIEW

Laboratory diagnostic procedures in the rheumatic diseases 2nd ed By 17 authors Edited by A S Cohen 433 pp Sw cr 137 Little Brown & Co Boston 1975

After seven years this unrivalled text has appeared in a second edition In 12 chapters it deals with most aspects of the laboratory diagnosis of rheumatic diseases Each chapter covers theoretical background clinical significance and detailed technical performance and ends with a very comprehensive list of references up to 1973 and occasionally even 1974

The book starts with 62 excellent pages on synovial fluid written by the editor s own group One agrees with the statement that too little use has been made of synovial fluid analysis in assessing the rheumatic diseases despite the accumulation of a large body of useful information Much of this information was gathered in the author s laboratory and is well presented together with a host of published work (241 references!)

The sedimentation rate is still regarded as a remarkably useful test even when compared with determination of individual plasma proteins The increase with age is tentatively attributed to subclinical inflammation but other explanations are more likely such as decrease in serum albumin A whole chapter is devoted to CRP though no mention is made of its probable role in phagocytosis The fourth chapter deals with rheumatoid factors and assays of humoral and cellular immune functions and is as up-to-date as the rapid progress in this field has allowed The same is true of the newly added chapter on complement

The 40-page chapter on the LE cell factor and antinuclear antibodies is written by a pioneer in ANA research and covers the subject up to DNA antibody tests and briefly mentions Ellings granulocyte specific ANA without assessing their use in clinical routine work

In dealing with streptococcal antibodies the significance of the ASO test is overemphasized This test has repeatedly been found positive in 20% of controls without evidence of recent streptococcal infection and in countries with a low incidence of rheumatic fever ASO testing probably mainly causes diagnostic and therapeutic confusion

In the following chapters serum uric acid serum enzymes and urinary excretion of products of connective tissue metabolism are well covered A good chapter on histopathology is included but one hopes to find one on arthroscopy in the next edition The book ends with the editor s chapter on the diagnosis of amyloidosis No more authoritative text on this subject is to be found in the literature today It is noteworthy that the Congo red test is still considered useful This test is widely neglected at least in Scandinavia

Every doctor dealing with rheumatic diseases should include this book in his library Its style and size makes a generous amount of information easily accessible and the interested reader will find the bibliographies after each chapter most helpful for further study

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Acta med scand Vol 199 327–329 1976

FOLLOW UP

What happened to the patient?

A Case of Carcinoid Syndrome Followed for Eight Years after Palliative Liver Resection

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In 1969 Aronsen et al (2) published three cases of carcinoid syndrome in whom liver resection of metastases was attempted In one of these patients the follow up has shown that the patient has had a long lasting remission in spite of the fact that the operation could not be radical Some data regarding this patient especially the signs of possible hyper insulinism were later discussed by Aronsen et al (1) We have thought that it may be of interest to report briefly on the further development of this disease as the literature contains only a few data regarding long term effects

CASE REPORT

The patient is a man born in 1909 He had all the typical symptoms of carcinoidosis with marked flushing severe diarrhoea some abdominal pain a weight loss of 8 kg during half a year and also symptoms of a gastric ulcer when he was admitted in 1967 He had no anaemia the serum bilirubin was 0 8 mg/100 ml Scintigrams of the liver disclosed diffuse infiltration of nodular tumours of varying sizes The infiltration was most pronounced in the inferior lateral aspect of the right liver lobe and in the lateral segment of the left liver lobe

The patient had a systodiastolic murmur consistent with an insufficiency and stenosis of the tricuspid valve His neck veins were prominent also in the sitting position His 5 HIAA values and changes in body weight are shown in Fig 1 and the results of heart catheterization in Table I In May 1967 a subtotal right lobectomy was performed but many metastases were seen also in other parts of the liver The weight of the resected specimen was 800 g No primary tumour could be found A high activity of tryptophan hydroxylase was found in the liver metastases (about 7 times normal) The postoperative course was rather stormy with marked increase in serum GPT (>800 U) The enzyme levels decreased during the following weeks

The patient was discharged in August He was then in a rather poor condition and had lost 20 kg in weight His 5 HIAA values had decreased very markedly and his flushing had disappeared The ECG findings before operation and three years later are found in a paper by Trell et al (9)

The patient was reexamined in Nov 1970 He had had a gastric ulcer but his general condition was much improved no diarrhoea only rare flushes He had been working for several years had remarried and seemed to be living a rather normal life He still had signs of tricuspid and pulmonary valvular heart disease

In Dec 1974 his general condition was still quite good and he was working His cardiac function had deteriorated somewhat and he had some swelling of the legs Light red flushing was observed on some occasions He had no jaundice but his left liver lobe was palpated three finger breadths below the arcus in the midclavicular line A lymph gland was felt in the right supraclavicular fossa Before the operation he had shown signs of fasting hypoglycaemia Blood sugar was therefore determined on three consecutive days in 1974 and the values were found to be 80 86 76 mg/100 ml Before the operation he had had a number of very low values the minimum being 35–47 mg/100 ml No blood sugar curve was determined in 1974 but before the operation he had a definitely pathological curve with an initial value of 49 no increase above 110 and a rapid decrease of 58

A cardiac biopsy of the right ventricle was taken together with the catheterization It showed signs of severe hypertrophy Liver scintigrams indicated no progress of the disease but the excretion of 5-HIAA had increased significantly (Fig 1)

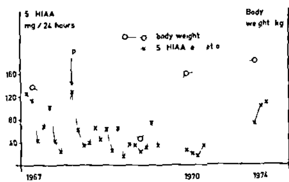


Fig 1 Results after operation

Up to now more than eight years after the operation the patient s condition has remained practically unchanged and he needs no continuous medical treatment nor has he shown any manifest signs of right heart failure

DISCUSSION

The surgical treatment in general of carcinoid tumours of the gastrointestinal tract has recently been reviewed by Morgan et al (4) In their series of 135 cases there were however only two patients who presented the picture of carcinoid syndrome and only four cases with liver metastases survived for ten years Wilson and Butterick (11) reported the benefits of palliative liver resection for symptomatic metastatic liver carcinoid in one case and Aronsen et al (2) reported three cases in whom this method was used One of the three cases reported by Aronsen et al (2) has later been described in detail (1) with particular reference to the possibility hyperinsulinism The patient has since been investigated twice with respect to his malignant disease as well as his earlier confirmed carcinoid heart disease As no long term follow up in such a case has been reported up to now the further development of the disease in this patient is described

Several reports the first by Thorson et al from this hospital (8) and most recently by Stephan and de Wit (6) Qizilbash et al (5) and Jagoe et al (3) have described the considerable improvement of carcinoid heart disease with right heart failure after removal of a functioning tumour in the ovary This improvement is attributed to the well established assumption that the substance or substances producing heart disease are broken down in the liver (7) The prerequisite for carcinoid heart disease is thus a functioning tumour in an organ the venous drainage of which does not pass through the liver

Table I *Hemodynamic findings on three different occasions*

RA=mean pressure in the right atrium RV=pressure in the right ventricle (systolic/diastolic) PCV=pulmonary capillary venous pressure (all in mmHg) Q̇=cardiac output (l/min) SV=stroke volume (ml/beat)

	1967	1970	1974
RA	13	14	13
RV	21/2–8	20/2–5	23/4–7
PCV	6	1	9
Q̇	3 66	3 67	3 48
SV	54	59	48

The effect of partial removal of a functioning tumour e g liver metastases upon established heart disease has so far not been described On the other hand it has been stated that once carcinoid heart disease is established it progresses slowly despite the removal of the tumour regardless of its location (10) Our patient does not seem to support the above statement Although the patient has a significantly increased mean pressure in the right atrium this has not shown any progress during eight years nor has the patient experienced any symptoms from it Apart from the carcinoid heart disease it is necessary to consider the other symptoms attributable to the growth of the malignant tumour Even if the carcinoid is slowly growing in itself it gives disabling symptoms such as frequent diarrhoea abdominal pain weight loss and general decline of the patient

The present case is unique in the respect that the patient has been reinvestigated twice after the partial liver resection and these investigations have not shown any progress either of the malignant disease itself or of the associated heart disease On the contrary his condition has improved to a great extent he has been and still is able to work almost free from his earlier symptoms Even if it is impossible to predict the course of the disease in this patient without any surgical treatment the natural history in other similar cases seems to justify partial liver resection in selected cases of malignant carcinoid tumours with liver metastases

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ANNOUNCEMENT

First International Symposium on HLA and Disease will be held in Paris France June 23–25 1976 on the topical subject of the relationship between HLA and disease Invited speakers will lecture on the basic principles (D Shreffler J Klein R Payne J J van Rood R Ceppellini C A Clarke) results already obtained (A Svejgaard P I Terasaki) clinical implications (J Dausset) fundamental hypotheses explaining the associations (R Zinkernagel W F Bodmer D B Amos)

Workshop sessions will bring together biologists and clinicians of every speciality rheumatology (D A Brewerton F Delbarre) neurology (T Fog F Lehermitte) dermatology (E M Farber J Civatte J Thivolet) endocrinology (J Nerup G Cathelineau) gastroenterology (W Strober I R Mackay J P Benhamou J Rey) allergology (A de Weck M N Blumenthal) immunopathology (H Kunkel M Seligmann) malignant diseases (M J Simon J L Amiel) other diseases (P J Morris, P Royer)

A special session will be devoted for discussion of the possible mechanisms of associations between HLA and disease (H O McDevitt F Jacob)

Chairmen J Dausset and A Svejgaard

Further information Congres Services 1 rue Jules Lefebvre F 75009 Paris France

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Recurrent and Reversible Cerebellar Ataxia with Concomitant Episodes of Hyperthyroidism

A New Autoimmune Syndrome

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ABSTRACT A new disorder with possible autoimmune background is described in a 67 year old man He had experienced episodes of cerebellar ataxia induced by infections over the last 40 years In 1963 he had thyrotoxicosis The patient underwent bilateral subtotal thyroidectomy Recently it has been possible to detect involvement also of his remaining thyroid gland, with findings compatible with hyperthyroidism concomitant with his cerebellar ataxia

The rapid development of clinical immunology and endocrinology in the last decade has great significance for clinical medicine The introduction of new immunological techniques and various hormone assays has increased the possibilities of making a correct diagnosis

The case presented here is an example of the use of these techniques in an attempt to search for the pathogenesis of an obscure syndrome This case has a unique combination of neurological and endocrinological symptoms As far as we know no similar case has previously been reported

CASE REPORT

The patient a man born in 1908 has no history of hereditary illness Until the age of 50 he was employed as a manual worker at various factories On several occasions he was forced to change jobs because of his illness For the last 12 years he has been a caretaker at a newspaper printing office He has not been exposed to any heavy metals or organic compounds regularly at work He had never used much alcohol and in recent years hardly any because of increasing dizziness after very small amounts

Except for a purulent knee joint inflammation at the age of 16 he remained well until 50 years old when he underwent a laminectomy at the L3–L4 level after a period of severe lumbar pain and neurological symptoms from the left leg Subsequently he developed a purulent spondylitis requiring a long stay in hospital

In 1961 febrile episodes and an ESR repeatedly above 100 mm/h motivated investigation This revealed a purulent maxillary sinusitis which was cured by aspiration and irrigation In 1963 the patient was admitted to hospital because of progressing nervousness tiredness sweating weight loss in spite of increased appetite and cardiac palpitations The laboratory work-up confirmed the diagnosis of thyrotoxicosis The patient underwent bilateral subtotal thyroidectomy During the following 10 years he was in fairly good health although he occasionally had episodes of illness as described below

In the beginning of 1973 he rapidly developed many symptoms nausea with vomiting diffuse abdominal pain chills and continued weight loss—about 10 kg in less than a year However the predominant symptoms were increasing disturbance of balance which made it impossible for him to maintain an erect position and obvious speech difficulties

When admitted in March 1973 he had a temperature of 38 5 C was emaciated and exophthalmus was present Dysarthria and grossly ataxic eye movements opsoclonus were present. He was unable to walk stand or even sit because of axial ataxia There was marked appendicular ataxia in all four extremities The preliminary diagnosis was that of malignancy with carcinomatous cerebellar degeneration (12) However the search for malignancy yielded no result Laboratory values were as follows Hb 13 7 g/100 ml WBC 8 000/mm^3 with 73% segmented neutrophils and 13% lymphocytes renal and liver function tests were normal ESR 89 mm/h Serum protein electrophoresis showed reduced albumin increased α_1 globulin and α globulin and an increased polyclonal γ globulin fraction The serum haptoglobin values were repeatedly high 451 and 385 mg/100 ml The bone marrow aspirate was not helpful The thyroid function tests at this time as well as later are reviewed in Table I

A thorough X ray survey was performed including lungs gastrointestinal tract kidneys skull spine and

Table I *Laboratory results with special reference to thyroid function and clinical course*

	April 1973	March 1974	May 1974	July 1974	Sept 1974	Oct 1974	Nov 1974
ESR (mm/h)	54–98	97–127	35	66	45	15	35
WBC/mm³	7 100	12 000	6 000		6 300	5 700	7 900
PBI (μg/100 ml)	8 1						
Serum thyroxine (nmol/l)		156	139	89		108	126
Triiodothyronine resin uptake (%)	132–202	150–158	113	104	76	85	96
TSH (μU/ml)	3 1	3 7		3 2		3 0	2 7
TSH response on TRH* infusion (μU/ml)		3 7–3 6–3 4–2 4			3 9–3 5–3 3–3 6		
Serum triiodothyronine (nmol/l)					3 3	2 4–2 8	3 0
Serum cholesterol (mg/100 ml)		110	138	196		235	
Serum triglycerides (mmol/l)		1 2	1 1	1 4		1 5	
Cerebellar ataxia	+	+	+				

* *Thyrotrophin releasing hormone (Ferring Malmo Sweden)*

some other parts of the skeleton All X rays were normal except old changes in the lumbar spine and a small concrement in one kidney A lumbar puncture revealed clear cerebrospinal fluid with total protein 48 mg/100 ml Thus the results of the investigations did not support the initial suspicion of malignancy

Within the course of a few weeks his condition improved After 3–4 weeks he was able to walk in the hospital corridor but with an unsteady gait During this hospital stay further penetration of the case history and discussion with the patient s wife revealed a very interesting story From about 20 years of age he had suffered numerous episodes similar to the present one but of increasing severity They always appeared after an infection particularly when this was accompanied by fever *The typical symptoms were unsteadiness of gait with inability to stand unsupported tremor nausea sweating palpitations and fever When the infection ceased all symptoms gradually disappeared within a few days up to a couple of weeks* Over the years the episodes seemed to become longer and lately some unsteadiness of the gait persisted between the attacks Because of this unique history and after the malignancy work up had proved negative the patient was subjected to close observation and immunologic screening Until the end of Feb 1974 he was in fairly good condition One week before admission he developed headache localized to the neck After a few days on March 1 he gradually became dizzy experienced difficulties in speaking and on the following day a fever of 39 8°C He was nauseated and started to vomit

The physical examination was identical to that in March 1973 except for a higher body temperature Neurological examination revealed scanning speech marked ataxia more in the lower extremities than in the upper horizontal nystagmus when turning the eyes to the sides and a vertical jerk nystagmus The tendon reflexes were normal vibration sense unimpaired The plantar reflexes were flexor

The laboratory investigations are reviewed in Tables I and II On this occasion the patient had a massive growth of Staphylococcus aureus in his urine and the level of antistaphylolysin titre was very high considered specific

Table II *Laboratory results with special reference to immunologic titres and clinical course*

	April 1973	March 1974	May 1974	July 1974	Sept 1974	Oct 1974	Nov 1974
ESR (mm/h)	54–98	97–127	35	66	45	15	35
Serum haptoglobin (mg/100 ml)	230–451				110		165
Antistreptolysin titre (U/ml)		63	55			164	200
Antistaphylolysin titre (U/ml)		10 1–40 3	7 1			5 7	3 7
Rheumatoid factor (latex fixation test)			Neg		Neg	1/40	Neg
Autoimmune antibodies against							
Antinuclear factor	1/25			Neg		Neg	
Thyroid cytoplasma					1/100		1/100
Mitochondria					1/100		
Renal tubuli (fluorescence)							1/25
Serum complement titre (H_{50})					13		16
Bacterial growth in the urine (Staphylococcus aureus/ml)		>100 000	>100 000				
Cerebellar ataxia	+	+	+				

The thyroid function tests showed high serum thyroxine and triiodothyronine resin uptake Serum cholesterol was 138 mg/100 ml

Corticosteroid therapy was started on March 6 1974 Prednisone was administered in a total dose of 30 mg a day A dramatic improvement of the symptoms was obtained after only a few days treatment The urinary infection was treated with trimethoprim sulphamethoxazole (On April 8 urine culture was negative) In the middle of March 1974 the most obvious neurological signs of cerebellar ataxia had disappeared and the patient was again walking The corticosteroid therapy was discontinued after one month on gradually tapering dosage The patient was discharged well on April 13 1974

He was readmitted on May 11 1974 because he had been acutely ill for two days with headache nausea vomiting shivering and fever and had symptoms of urinary infection Physical examination was similar to that during previous episodes A urine culture showed significant growth of Staphylococcus aureus Further results of laboratory work up are reviewed in Tables I and II The treatment this time was identical to that in March 1974 with both prednisone and trimethoprim sulphamethoxazole All symptoms improved rapidly after the institution of therapy

A more complete investigation of thyroid function was made as reviewed in Table I Administration of thyrotrophin releasing hormone resulted in a markedly impaired thyroid stimulating hormone (TSH) response TSH values were repeatedly normal A biopsy from the thyroid gland revealed a picture compatible with hyperactivity with enlarged polychromatic nuclei (in March 1974) In March 1973 the biopsy had been normal There was an undisputable increase in the patient s exophthalmus In 1970 the Hertel value had been 16/18 (right/left) in May 1974 20/21 and in Oct 1974 22/20 No long acting thyroid stimulator activity was found when measured in Nov and Dec 1974

In an attempt to prove the autoimmune pathogenesis many antibody titres were studied during the follow-up A survey of these determinations is given in Table II

After May 1974 when he had the last episode (prednisone was discontinued in the middle of June) the patient has been in good condition He has not had any infection since then

However he has continuously shown autoimmune activity even during this apparently healthy period The antibody titres against cytoplasmic thyroid antigen were positive in Sept and Nov 1974 Antibodies against mitochondria were positive in Sept 1974 and against kidney tubuli in Nov 1974 These positive titres were accompanied by very low complement levels These findings were compatible with a continuing subclinical immunological activity Antibodies against cerebral tissue were negative in Nov 1974

The cerebrospinal fluid showed total protein 50 mg/100 ml (an upper normal value) There was an increase in the ferogram in the α_2 zone a moderate increase of τ proteins and a slightly increased polyclonal γ fraction At the same time Oct 1974 the serum immunoglobulins were IgG 900 IgA 260 and IgM 70 mg/100 ml (all within normal limits) ESR was 15 mm/h

DISCUSSION

The patient had a remarkable history For more than 40 years he repeatedly had symptoms of cerebellar ataxia elicited by infections with fever These episodes forced him to stay in bed at first for one or two days but lately for longer Three episodes have been seen by us in hospital and they were clinically very impressive

Acute cerebellar ataxia associated with infection is considered to be an unusual neurological syndrome mostly affecting children between one and four years of age (4) It has also been described in adults (3) To our knowledge a relapsing type of cerebellar ataxia over such a long time has not been described before

The aetiology of many cases of acute cerebellar ataxia remains undetermined although the syndrome has accompanied various infectious diseases e g rubeola rubella mumps varicella infectious mononucleosis and influenza (13) It has also followed the administration of smallpox and measles virus vaccines (11) The suggested causes have been either a focal brainstem encephalitis due to toxic or infective agents or an autoimmune response of the nervous system to a number of different agents (1) In the present case there is some evidence for an autoimmune mechanism Some of the antibody titres studied were positive Furthermore there was a remarkable improvement when corticosteroids were given

Antistaphylolysin titres were very high and urine cultures repeatedly showed significant growth of Staphylococcus aureus The question then arose whether this antibody could cross react with cerebellar tissue and precipitate the symptoms The picture became still more complex when the patient also had recurrent clinical symptoms of hyperthyroidism along with the neurological findings The increasing evidence that hyperthyroidism may be an autoimmune disorder (7 8) fits well in our patient The possibility of one or more antibodies with different target organs such as the thyroid and the cerebellum must be kept in mind The combination of hypothyroidism and cerebellar ataxia is well known (9 10) However the cerebellar symptoms are probably caused by the disordered metabolic state in myxoedema as they are reversible with substitution therapy Our patient has never been myxoedematous but has had clear clinical symptoms and laboratory evidence supporting hyperthyroidism

Cerebellar ataxia has been reported to follow episodes of protracted fever (5 6) In these cases however the temperature was extremely high the patients were comatose during hyperpyrexia and the cerebellar ataxia was irreversible Therefore we find it very unlikely that the elevated body temperature per se was responsible for the reversible cerebellar symptoms in our patient

The infection that initiated the episode in 1974 was a staphylococcal urinary infection However many different infectious agents have been reported in children (10 13) Therefore it is likely that other agents caused the earlier ataxia in our patient particularly as he has generally had the episodes after upper respiratory tract infections

Finally we consider it unlikely that the anti staphylolysin in itself is the causative factor in this case since the titre had normalized at the same time as there was a steady consumption of complement when measured in late 1974 indicating autoimmune activity

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Temporary Changes in the Renal Function Following Streptokinase Therapy

A Case Report

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Streptokinase has been widely used in the treatment of venous thrombosis Although complications such as bleedings febrile reactions allergic and anaphylactoid reactions or emboli have been observed during treatment changes in the kidney function have not been mentioned in previous articles This paper reports on a case with temporary changes in the renal tubule function as shown by radiorenography and osmolality examinations The possibility that the changes are due to immune reactions is discussed

CASE REPORT

Following a car accident a 50-year-old man was admitted to Huddinge Hospital He had fractures of the right 9th–11th ribs No pneumothorax or infiltrates in the lung were present The laboratory examinations showed microscopic haematuria (but no haemoglobinuria) normal ESR and normal plasma creatinine values

During the following days the patient because of a retroperitoneal haematoma developed a transient paralytic ileus Urinalysis and IVP showed normal kidney function and outline One week after admission the patient developed a thrombus in the right calf (verified by ascending phlebography) Signs of pulmonary embolism were also present and a lung scintigram revealed small emboli However the patient rapidly recovered on heparin treatment (Heparin Vitrum Sweden) 50 000 IU daily for 7 days and was discharged after 3 weeks

A week later the patient returned with a four-day history of severe pains in his right leg The clinical diagnosis of venous thrombosis in the right calf and in the distal part of the thigh was verified on a phlebogram Laboratory examinations showed an increased ESR Plasma creatinine was normal Treatment with heparin (20 000 IU in 12 hours) was immediately started As a severe progress of the thrombus was noted on the following day the treatment was changed to streptokinase (SK) The patient was given Kabikinas® (Kabi Sweden) in an initial dose of 500 000 IU in 500 ml saline i v during 60 min followed by 100 000 IU every hour for the next 67 hours Every 12th hour 50 mg hydrocortisone (Solu-Cortef® Upjohn) was given Forty-eight hours after ended SK treatment the hydrocortisone doses were gradually diminished

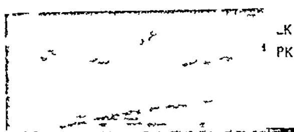
During the treatment the patient once developed a chill but no other complications were noticed Three hours after discontinuation of SK treatment a descending phlebography confirmed the clinical data and showed a total disappearance of the fresh thrombus in the calf and thigh The old thrombus in the calf was unaffected Heparin treatment (45 000 IU daily) was again started and continued for one week while dicumarol (100–150 mg daily) was given continuously during the next three months Urinalysis urine osmolality and plasma creatinine were normal immediately after SK treatment

Four days later the patient complained of pains in the loins and new investigations of kidney function were performed Urinalysis now revealed slight haematuria and glycosuria. IVP was normal Plasma creatinine was slightly increased and urine osmolality was only 160 mosmol/l (normal range 450–800) although blood osmolality was normal A radiorenogram showed a normal glomerular uptake but there were signs of postglomerular obstruction on both sides (Fig 1) The following week the patient s symptoms improved microscopic haematuria disappeared and urine osmolality gradually increased to 240 mosmol/l ESR increased from 35 to 80 mmHg After three weeks the radiorenogram was normal as was also the urine osmolality ESR did not return to normal for another month

The antistreptokinase titre was still normal (1 160 U) on the third day after the start of SK treatment High values were observed on the 10th and 17th days (57 000 and 50 000 U respectively) Six weeks after the start of SK treatment the titre was 14 000 U

DISCUSSION

Side-effects of SK treatment have been reported (2 4 5 6) Kidney changes during SK treatment have



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hule a body ct nase (AS t g ven to h ha e ASK t tre k y on h 9th y tarting SK t eatm al rea es t a n r 1 n 4–8 weeks It th n u cr ases ch g t c g nal level after 3 6 months (5) In t e cno t d ca e t ASK titre was ra s 1 on the 10 h day nd o m l after 3 months The rise in titre paralleled the renal dys function The history of this pat ent does not support streptococcal infections as an explanation of the increased ASK titre

Temporary changes in renal funct on have been mentioned following SK treatment in a pat ent w th deep venous thrombosis and thrombos s at the venous connection of a transplanted k dney (1) That patient was being treated with immunosuppressi e therapy and it seems more l kely that the changes were due to the disturbance of the venous drainage of the kidney

The complicat on in our patient ind cates the necessity of following the renal function during SK treatment

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Clinical Features in Poisonings by Tricyclic Antidepressants with Special Reference to the ECG

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ABSTRACT Clinical variables, and especially their relation to the ECG, have been studied in 153 cases of poisonings by tricyclic antidepressants (TCA) The mean age of the patients was 34 years Amitriptyline poisoning accounted for 112 (73%) of the cases and the mean dose ingested was about 1000 mg Coma was present in 87 patients (57%) and on admission 40 (26%) had a systolic blood pressure (BP) below 100 mmHg The systolic BP on admission was significantly lower ($p<0\ 001$) and the hart rate (HR) higher ($p<0\ 001$) than when the patients left the ward Apart from an increased HR (≥90 beats/min) which was present in 73% of the cases the most characteristic ECG change was a QRS prolongation (≥0 11 sec) this being found in 42% of the cases About the same proportion displayed a QT prolongation and 28% had a prolonged PQ time The mean of the QRS times was 0 11 sec Unlike the QT time, the QRS time was not correlated to HR Statistical analysis of the material with regard to clinical variables (dose of TCA, BP, coma duration, etc) showed that the QRS time was closely related to the severity of poisoning Five patients (3%) died, all of whom already on admission demonstrated advanced ECG changes with arrhythmias and a mean QRS time of 0 19 sec Excluding dibenzepine poisonings (4 cases all fatal), the mortality rate was 0 7% The importance of high initial preparedness for cardiac complications is pointed out, as is the value of the QRS time as a guide to the severity of poisoning

The first tricyclic antidepressant (TCA) to be introduced in psychiatric practice was imipramine in 1954 Since then several derivatives of TCA have been synthetized e g amitriptyline (AT) and their use has become extensive especially during the last decade In Sweden the total sale of TCA tablets in 1970 exceeded that of barbiturates by 64% (19)

A few years after the introduction of TCA minor therapeutic side effects from the cardiovascular system were reported such as hypotension and ST T changes in the ECG (17) Since then there have been numerous case reports about serious effects with marked ECG changes and sometimes fatal outcome as a result of poisonings with TCA (7 8 12 16 30) but there have not been many accounts of large materials (9 11 14 20) In the French literature in particular attention has been drawn to marked QRS prolongations as a potential risk in poisonings by TCA (9 11 14 21) However the relationship between ECG changes and other clinical parameters has not been reported in detail It has proved impossible to determine the LD 50 for humans owing to the difficulty of obtaining the necessary information about ingested doses of the drug (11)

On the basis of 153 cases of TCA poisonings it is the aim of this paper to report on the frequency of different clinical symptoms with special reference to the incidence of ECG changes It was also hoped that the study might provide information about the relationship between ECG pattern and clinical state as a means of estimating the severity of the poisoning at an early stage from the ECG

MATERIAL AND METHODS

This retrospective study includes 153 consecutive patients 64 men and 89 women with TCA poisoning admitted to the Intensive Care Unit (ICU) of Sodersjukhuset Stockholm between Jan 1 1968 and May Two poisonings with an ingested dose below excluded from the original sample as well lacking diagnostic ECG recordings T patients was 34 years (range 14–66) (Fig

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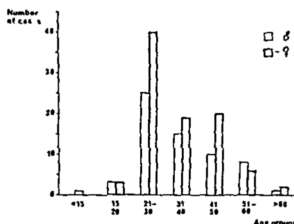


Fig 1 Age and sex distribution of 153 cases of poisonings by tricyclic antidepressants

was based upon supportive therapy according to the conventional Scandinavian method (6 19)

AT was the predominant drug being the only one taken in 41 cases and combined in a further 71 cases with other drugs or alcohol Imipramine and nortriptyline the most frequent among other derivatives of TCA were the only drugs in 10 and 7 cases respectively There were 24 cases of mixed TCA poisonings other than AT Urinalysis for neuroleptics and blood tests for barbiturates by spectrophotometric methods were performed routinely in the Central Chemical Laboratory but as for TCA there were only 17 patients in whom the plasma concentration (mean 1 9 μg/ml) was determined by gas chromatography In 14 cases involving barbiturates the plasma barbiturate concentration was 2 9 μg/ml Suspicion of alcohol intake was confirmed in all the 42 patients in whom blood tests for cohol were performed The mean blood concentration as 1 5‰ In the event of discrepancies in the anamnestic formation the type of poisoning was classified from the chemical analysis Disregarding differences in the relative potency of different TCA compounds the average dose of TCA ingested was calculated to be 1 048 mg The distribution of doses is shown in Fig 2 Due to lack of information the dose could not be calculated in 52 cases The interval between tablet ingestion and admission to the ward averaged 7 hours (range 1–72)

Plasma electrolytes were analysed by a conventional AutoAnalyzer The patients stayed an average of 2 8 days in the ICU

The ECG recordings used for analysis of time intervals were generally performed less than one hour after admission Both standard and chest leads were recorded paper speed being 50 mm/sec Time intervals were measured in the lead where they were best defined usually CR_2 The QRS duration measured was referred to one of the following groups <0 10 0 10 0 11 0 12 and >0 12 sec QRS times≥0 11 sec were defined as prolonged Heart rate (HR) above 90 beats/min was defined as tachycardia PQ and QT times were compared to normal values corrected for HR (13) A chest lead ECG was usually monitored during the comatose period However no detailed information is available about the frequency of various types of arrhythmia Blood pressure (BP) was measured with the cuff method at least every hour during the early phase of the poisoning the intervals being prolonged as the patients improved Systolic BP below 100 mmHg was defined as hypotensive

Clinical data during the initial stage have been compared with those during a later period of 6 hours referred to as the final period when most patients were awake and without apparent signs of poisoning This latter set of values has been used as "control values Unless otherwise stated all values given in the following refer to the initial period of poisoning The lowest values of HR and BP were chosen during the respective periods except for the initial HR which was determined from the ECG Arterial pH PO_2 and PCO_2 were measured by electrode technique (Radiometer equipment) at 37°C Only blood gas values from patients breathing spontaneously and without oxygen supply at the time of blood sampling (70 cases) were included

Statistical analysis was performed in two ways Firstly clinical variables were compared according to linear regression analysis Secondly the material was divided into paired groups in which the means of different variables were compared according to the Mann Whitney test (15) which allows for uneven distributions The calculations were made with the aid of an IBM 360/75 computer

RESULTS

The mean values of the variables studied are shown in Table I

Cardiovascular changes

HR The initial HR averaged 97 beats/min (range 50–145) in 112 cases (73%) the HR was ≥90

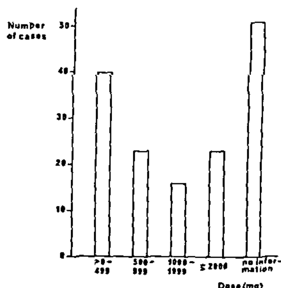


Fig 2 Incidence of different dose ranges in poisonings by tricyclic antidepressants

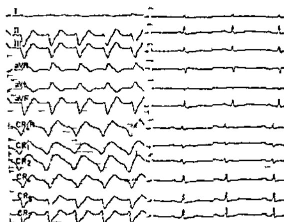


Fig 3 Advanced ECG changes in a woman aged 29 who had taken a fatal amount of the tricyclic antidepressant dibenzepine *Left* on admission *right* one day later Paper speed 50 mm/sec

beats/min The final value was 82 beats/min (range 50–125) measured just before the patients left the ward The difference is highly significant ($p<0.001$) The cardiac rhythm was of sinus type in all but 4 patients who demonstrated nodal or ventricular rhythm of varying frequency No other arrhythmias were observed on the diagnostic ECG recordings except for occasional ventricular extrasystoles in a few cases

ECG A case with advanced ECG changes resulting from dibenzepine poisoning is presented in Fig 3 The mean QRS time in the material was 0 11 sec (range 0 06–0 30) There were 65 cases (42%) with a QRS time of 0 11 sec or more The distribution of QRS times is shown in Fig 4

The PQ time averaged 0 18 sec (range 0 13–0 30) which is at the upper normal limit after allowing for the increased HR In 43 cases (28%) the PQ time was prolonged in relation to HR (13) The QT time which averaged 0 37 sec (range 0 29–0 65) was prolonged in 75 cases (49%) (13) The QT times were prolonged compared to a normal material (13) as demonstrated by the significant difference ($p<0.01$) between the two regression lines in Fig 5 There was no significant linear correlation between PQ and QRS times (Table III) but according to the results in Table II increased mean values of QRS were accompanied by increased PQ times The QRS time was not significantly correlated to HR

The ST segments varied somewhat in configuration and there were elevations as well as depressions but most patients presented no specific changes The T waves were often somewhat broad and flattened in connection with marked QRS prolongation

Blood pressure Forty patients (26%) were hypotensive with a systolic BP below 100 mmHg The mean initial systolic BP after arrival at the ICU was 108 mmHg and the final value was 118 mmHg which is significantly higher ($p<0.001$) The corresponding diastolic BP values were 74 and 75 mmHg

Other clinical changes

Coma was present in 87 patients 27 were comatose for more than 24 hours 33 for 12–24 hours and in 27 the coma lasted 12 hours or less Mixed poisonings were twice as common as pure TCA poisonings among the comatose patients and accounted for half of the soporous or awake patients Excluding the five patients who died the mean duration of coma was 23 hours

Body temperature This had fallen initially to an average of 35 9°C (range 25 8–38 4) and rose during treatment in the ward to an average maximum of 37 6 C (range 34 4–39 7)

Table I *Clinical data in 153 patients with poisonings by tricyclic antidepressants*

BT=body temperature SBP systolic BP DBP=diastolic BP

	n	Mean	S D	Range
Age (y)	153	34 1	11 3	14 0–66 0
TCA dose (mg)	102	1 048	1 160	150–8 000
Ingestion—admission time (h)	127	7	8	1–72
Duration of coma (h)	87	26	24	3–160
Min BT (°C)	*151*	*35 9*	*1 4*	*25 8–38 4*
Max BT (°C)	147	37 6	0 7	34 4–39 7
Duration of care (d)	153	2 8	2 4	1 0–17 0
Initial SBP (mmHg)	153	108	17	50–150
Initial DBP (mmHg)	153	74	13	15–100
Final SBP (mmHg)	153	118	16	65–160
Final DBP (mmHg)	153	75	11	40–110
Initial HR (beats/min)	153	97	17	50–145
Final HR (beats/min)	151	82	13	50–125
PQ time (sec)	149	0 18	0 03	0 13–0 30
QRS time (sec)	153	0 11	0 03	0 06–0 30
QT time (sec)	153	0 37	0 05	0 29–0 65
pH	70	7 35	0 07	7 18–7 57
PaO_2 (mmHg)	69	70 9	17 1	28 0–95 0
$PaCO_2$ (mmHg)	70	37 9	8 9	13 0–60 0
Serum K^+ (mEq/l)	145	4 0	0 6	2 3–6 4
Serum Na (mEq/l)	133	143 1	4 7	130 0–161 0

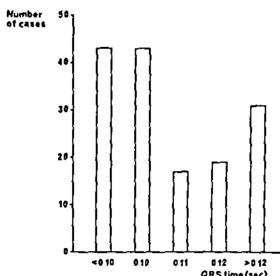


Fig 4 Frequency of different QRS times in poisonings by tricyclic antidepressants

pH and blood gases Among 70 patients with spontaneous breathing acidosis (pH<7 35) was present in 31 In 14 the pH value was <7 30 and in one it was 7 18 The acidosis was respiratory in 4 cases and combined respiratory and metabolic in 8 A mild metabolic acidosis dominated among the remaining acidotic patients A majority of the patients (33 cases) had a normal pH and 6 had alkalosis (pH>7 45) The mean pH was a low borderline value (7 35) Arterial PO_2 was generally low with a mean of 71 mmHg and only 16 patients (23 %) had values above 85 mmHg

Serum K^+ and Na^+ There were 22 patients (15 %) with decreased serum K^+ ($K<3$ 6 mEq/l) and only one had an increase (>5 3 mEq/l) Serum Na^+ was increased ($Na^+ >145$ mEq/l) in 12 patients (9 %) and decreased in 4 The mean values $K^+=4$ 0 and $Na^+=143$ mEq/l were within normal/limits

Respiration Thirty five patients (22 %) had respirator treatment during part of the course of the poisoning

Convulsions occurred in 17 patients (11 %) about half of whom demonstrated seizures of epileptic type

Relationships between some clinical findings

Table II presents the material divided into paired groups with special regard to the amount of drug ingested and QRS duration The means of the respective pairs of groups have been compared with regard to the incidence of various clinical findings Table III shows the results of correlating the same variables to each other according to linear regression analysis

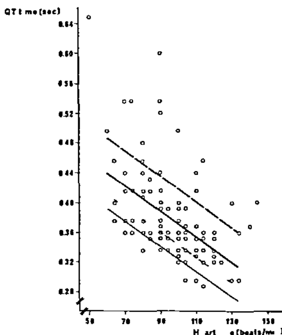
Table II *Total material of poisonings by tricyclic antidepressants (n=153) divided into paired groups for comparisons between the means of clinical variables*

The figures refer to the statistical significance (1=$p<0$ 05 2=$p<0$ 01 3=$p<0$ 001) + and − to the first (left) groups and indicate an increased or decreased mean value in relation to the second (right) groups Abbreviations as in Table I The variables serum K and Na which showed no significant changes are not included

Materials				Variables						
n_1		n_2		Age	Duration of coma	TCA dose	Min BT	Initial HR	Final HR	Initial BP
Males	64	Females	89							3+
Age <40 y	106	Age ≥40 y	47				1+	2+		
AT only	41	Mixed drugs	112							
TCA 0–499 mg	40	TCA 1 000–1 999 mg	16		2−			1−	1−	
TCA 0–499 mg	40	TCA ≥2 000 mg	23		3−			1−		2+
TCA 500–999 mg	23	TCA ≥2 000 mg	23		3−					2+
TCA 1 000–1 999 mg	16	TCA ≥2 000 mg	23							
ECG normal	55	ECG pathol	98		3−	3−	1+			
QRS <0 10 sec	44	QRS=0 10 sec	44				1+			
QRS <0 10 sec	44	QRS=0 11 sec	16	1−		1−	1+			
QRS <0 10 sec	44	QRS ≥0 12 sec	49	1−	3−	3−				2+
QRS=0 10 sec	44	QRS ≥0 12 sec	49		2−	3−				1+
QRS=0 11 sec	16	QRS ≥0 12 sec	49							
QT normal	78	QT prolonged	75		3−	3−	2+			1+
Awake—soporous	66	Coma	87			3−	3+	1−	1−	3+
Convulsions	17	No convulsions	136		3+	2+				
Respirator	35	No respirator	118			3+	3−			3−

There were a number of signif cant positive correlations such as those between dose and the variables PQ QRS and QT t me Dose and in t al BP correlated negatively There was no s gn ficant correlat on between dose and the in tial HR n contrast to the positive correlat on to the final HR The QRS t me was not s gn f cantly correlated to age or t me of coma Nor was there a correlat on between the durat on of coma and time of care though the mean values of these two variables differed s gnif cantly between pat ent groups w th QRS<0 10 and those with QRS>0 1? sec (Table II) Serum concentrations of K and Na were not correlated to either QRS QT or PQ t mes Sex and age d d not influence the variables stud ed except for n t al BP which was lower in women (Table II) Nor were there any statistical d fferences between pat ents who had ingested AT only and the cases w th mixed poison ngs the latter group includ ng a l m ted number of TCA poison ngs other than AT Pat ents with coma or pathological ECG showed increases of variables l ke t me of care dose of ingested TCA and QRS t me when compared to pat ents who were awake or lacked ECG changes The same was true of patients who suffered from convuls ons or had respirator treatment The con centrat ons of TCA n blood and urine showed no detectable relationsh p to the dose ingested or the degree of ECG changes

PQ time	QRS time	QT t me	Durat on of care
1	1	3	
1	2		2
2	3	2	3
	3	2	2
	2	1	
3	3	3	3
2		2	2
3		1	1
3		3	3
3		3	1
3	3		3
	3		3
1+	3+	3+	3+
1+	3+	3+	2+



F g 5 Relat on between *QT time* and *heart rate n* po son ngs by tricycl c antidepressants (*r* 0 5?) with a regress on l ne (lowest) from a normal material (13) for comparison The broken lines nd cate 1 S E M

Fatal cases

The total mortality rate was 3% (5 cases) All four cases of d benzep ne (Neodal t®) po son ng had a fatal outcome Early informat on to the man ufacturer (24) that dibenzepine might be an espe cially toxic TCA compound contributed to the w thdrawal of th s drug from the Swed sh market One pat ent d ed from AT poison ng Exclud ng the four d benzep ne poisonings the mortal ty rate was 0 7%

All the fatal cases already had cardio-resp ratory compl cations such as arrhythm as aspirat on or acidosis on adm ssion to the ICU On an average the dose ingested in the fatal cases was more than three t mes larger than that for the total material The cases with a fatal outcome were characterized by low in tial mean BP (76 mmHg) low body temperature (34 7°C) and a lower heart rate (83 beats/m n) than the average for the material The average QRS and QT times were markedly in creased (0 19 and 0 55 sec respect vely) compared w th the ent re material Both the conf guration of the QRS complexes and the kind of arrhythmias present varied

Table III *Results of correlation tests between some clinical variables in tricyclic antidepressant poisonings in the left column and the same set of variables in the horizontal top row*

The calculation was made with the aid of linear regression analysis The figures in the diagram refer to the statistical significance according to the correlation coefficient r ($1 = p < 0.05$ $2 = p < 0.01$ $3 = p < 0.001$) Positive and negative correlations are indicated by + and − respectively *0 indicates that the correlation test was not significant* Abbreviations as in Table I

	TCA dose	Age	Initial BP	Initial HR	Final HR	Duration of coma	Min BT	PQ time	QRS time	QT time	Serum K	Serum Na⁺	Duration of care
TCA dose	×		1−	0	2+	0		2+	3+	3+			3+
Age		×							0				
Initial BP	1−		×			2−	1+						
Initial HR	0			×		0			0	3−			0
Final HR	2+				×				0				
Duration of coma	0		2−	0		×	0		0				
Min BT			1+			0	×						1+
PQ time	2+							×	0		0	0	
QRS time	3+	0		0	0	0		0	×		0	0	0
QT time	3+			3−						×			
Serum K⁺								0	0		×		
Serum Na								0	0			×	
Duration of care	3+			0			1+		0				×

DISCUSSION

According to several reports severe poisonings by TCA are consistently accompanied by ECG changes often with broadened and distorted QRS complexes (3 9 11 14 25) This is in agreement with the present study in which 64% of the patients had pathological ECG changes These took the *form of QRS broadenings in 42% and the remainder* were dominated by slight or moderate PQ and QT longations Noble and Matthew (20) reported ly a few ECG changes of this kind but their included mainly mild poisonings the mean ingested dose being about half that in this material

In severe TCA poisonings the ECG pattern is relatively characteristic and the ECG may be useful in distinguishing these poisonings from other drug poisonings (2) As young people dominated the present material the incidence of preexisting ECG changes was probably low The most severely ill patients i e those with convulsions coma respirator treatment or fatal outcome were characterized by marked and highly significant QRS prolongation Also there was a significant correlation between dose intake and QRS time (in cases where the approximate dose was known) Thus in the absence of previous ECG changes the degree of QRS prolongation is a measure of the severity of the poisoning The lack of significant correlations to the duration of coma and time of care may be explained by factors other than the TCA effect itself In patients with a markedly prolonged QRS time however there was a significantly higher incidence of prolonged coma

Eighty-eight patients with TCA poisoning had QRS times within the normal range (≤0 10 sec) but several showed a decreased QRS time within a few days after drug intake Thus the incidence of TCA induced QRS prolongations is obviously *higher than 42% which was the frequency of* QRS≥0 11 sec This illustrates the diagnostic value of repeated ECG recordings in patients with suspected TCA poisoning Even marked QRS prolongations generally returned to normal within a week Patients with a QRS time of 0 11 sec did not differ from those with longer QRS times regarding the variables tested which means that a QRS time of no more than 0 11 sec may indicate a serious TCA poisoning

The QT times could not be measured so exactly owing to the difficulty of delimiting the end of the T wave from the U or P waves This makes the QT times less reliable in estimating the degree of TCA poisoning Furthermore the percental increase in QT time was comparatively small and thus less obvious than for QRS However the QT time corrected for HR was significantly prolonged and the degree of prolongation was correlated to parameters reflecting the severity of TCA poisoning

PQ prolongation is another less frequent effect of TCA poisoning but for reasons similar to those

described for QT the PQ time is a less useful measure of the degree of poisoning

Sinus tachycardia which has been attributed to an atropine like effect of TCA (3 20) was another common finding in this material The dose was correlated only with the final HR This may indicate a residual anticholinergic effect of TCA In the initial stage the patients were probably submitted to more complex autonomic and direct toxic influences

Arrhythmias other than sinus tachycardia are considered to be a common complication of TCA poisoning possibly because arrhythmias are frequently found in cases with fatal outcome Contrary to this but in agreement with another survey (20) no arrhythmias apart from sinus tachycardia were recorded among the surviving patients in this material In four of the patients who died however there was arrhythmia of nodal or ventricular type It seems that a massive dose of 1 5–2 0 g or more generally is a prerequisite in acute poisonings for the development of serious arrhythmias in adults This agrees with the review of Davis et al (7) where the mean fatal dose for six AT poisonings was 2 2 g

A direct toxic effect of the drug combined with an increased adrenergic strain (4 10 28) possibly accounts for serious arrhythmias These often take the form of a nodal rhythm with aberrant intraventricular conduction or a ventricular tachycardia Extrasystoles may be present as well In one of the fatal cases the QRS time was markedly reduced just before the fatal arrhythmia occurred (Fig 3) The same experience was reported in a case by Sedal et al (25) This indicates that the QRS prolongation per se is not necessarily responsible for the fatal outcome During the final stage a slow rhythm of idioventricular type has been reported (7 21)

TCA in lower doses have been shown to possess quinidine like antiarrhythmic properties (22 26) an effect which seems to overrule other potentially arrhythmic properties of TCA in poisonings of light or moderate degree

It has been suggested that hypokalemia is a frequent finding which may cause prolongation of the intraventricular conduction time in TCA poisoning (18) Correlations between electrolytes and ECG or other clinical variables were not found in this material This agrees with a recent study in animals which gave no support for electrolyte disturbances as a cause of the ECG changes (29) It is uncertain whether the incidence of hypokalemia in the present TCA poisonings (15%) differs from that among other patients in the ICU The same reservation applies to the frequency of acidosis on admission As the potassium values in this study were based on blood samples taken on an average seven hours after drug ingestion one cannot rule out true electrolyte effects under the persistent influence of TCA No analysis of electrolytes in urine was performed

AT is reported to have a high affinity to the myocardium (5) Fournier (9) found no correlation between ECG changes and blood concentrations of imipramine and suggested that the blood concentration may not accurately reflect the myocardial fixation of the drug He also stated that blood concentration data give more information about the expected duration of the poisoning than about its immediate seriousness As in the case of ECG no correlation has been found between dose and blood concentration in the present or earlier work (9) Factors such as uncertainty regarding the ingested dose vomiting and interindividual differences in pharmacokinetics (1) may play a role Using controlled conditions and a sensitive blood test method it was possible to show a relationship between plasma level of nortriptyline and therapeutic effect (31)

TCA may provoke hypotension (17 23) This is supported by the present finding that the BP was inversely correlated to the dose

A sudden deterioration may occur in acute TCA poisonings and the patients should be supervised in an ICU if the ingested dose is suspected of exceeding 1 g Frequent or continuous ECG recordings should be performed and provide an easy way of following the course of the poisoning Continuous supervision by a cardiac alarm system is desirable for the detection of arrhythmias In addition to i v fluid infusions in comatose cases measures such as prophylactic endotracheal intubation in cases with increasing or broad QRS times make the situation easier to handle in the event of sudden arrhythmia with hypotension or epileptic seizures High preparedness is of the utmost importance for a low mortality rate in severe cases Regarding several alarming reports of TCA poisonings it is interesting to note that the mortality rate in this material does not exceed that of hypnotic poisonings (6 27) In fact if dibenzepine poisonings are excluded the present mortality rate was about 0 7%

Though the QRS time has proved to be valuable in the assessment of TCA poisonings it should be used not alone but together with other relevant clinical signs

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Liver Biopsies in Epileptics during Anticonvulsant Therapy

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ABSTRACT Liver function tests, performed in 11 epileptics under antiepileptic treatment for 10–35 years, showed a slight increase in serum alanine aminotransferase in six patients and a marked increased level of serum alkaline phosphatases in four Liver biopsies revealed few uni or paucicellular necroses in five patients Granulomatous hepatitis was found in one patient in whom sarcoidosis was later diagnosed None of the biopsies showed signs of permanent liver damage

In diphenylhydantoin (DPH) treatment hypersensitivity hepatitis is a well known phenomenon presenting itself a few weeks after the institution of drug administration (10) Otherwise hepatotoxicity of DPH is undocumented However the findings of increased serum alkaline phosphatase activity (both liver and bone isoenzymes) (1 9 18) and serum alanine aminotransferase activity (1) could be an indication of liver damage in patients during long term DPH therapy In the present investigation hepatological studies including liver biopsies were performed to elucidate this problem

PATIENTS AND METHODS

Eleven epileptics under antiepileptic treatment for 10–35 years were investigated Their age and sex distribution and the duration of antiepileptic treatment are shown in Table I The patients had no symptoms or clinical signs of liver disease and apart from anticonvulsant drugs none of them received any medication All epileptics received DPH the mean total dose being 1115 g (range 236–2022) Three epileptics (nos 2 7 9) had been treated only with DPH the others had received DPH in combination with one or more of the following drugs phenobarbitone primidone and carbamazepine

Determinations of serum bilirubin (7) serum alanine aminotransferase (3) serum aspartate aminotransferase (3) serum alkaline phosphatase (3) plasma prothrombin time (16) and serum albumin (20) were performed together with the bromsulphalein (BSP) retention test (23) Needle biopsy of the liver was performed by the method of Menghini The specimens obtained were fixed in neutral phosphate buffered 4% formaldehyde Paraffin sections were stained with hematoxylin-eosin Van Gieson trichrome Masson PAS and Gordon and Sweet s reticulin stain Sections from all biopsies were assessed independently by two observers and then reassessed jointly

RESULTS

The results of the biochemical tests are shown in Table I Serum aspartate aminotransferase was essentially normal in all patients while serum alanine aminotransferase was slightly increased in six and serum alkaline phosphatases markedly increased in four patients All patients had normal serum bilirubin and normal plasma prothrombin time In one patient the albumin concentration in serum was below normal The BSP retention test was normal in all patients

The histological observations in the 11 biopsies are summarized in Table II One biopsy (no 1) showed sarcoid granulomata and moderate lymphocyte infiltration in the portal spaces This biopsy specimen also contained a few focal necroses in the parenchyma and focal lymphocyte infiltrations as well as focal proliferations of Kupffer cells were seen in the lobules Further investigations have shown additional signs of sarcoidosis and all inflammatory changes observed in the biopsy specimen may be

Though the QRS time has proved to be valuable in the assessment of TCA poisonings it should be used not alone but together with other relevant clinical signs

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Anticonvulsant Osteomalacia Determined by Quantitative Analysis of Bone Changes

Population Study and Possible Risk Factors

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ABSTRACT Material has been obtained by biopsy from the right iliac crest of 60 adult epileptic out patients receiving chronic anticonvulsant therapy with diphenylhydantoin (DPH), either in single drug or combined drug regime, and of 16 controls with the same distribution by sex and age Four (7%) of the epileptics were hypocalcemic and 25 (42%) had elevated serum alkaline phosphatase values A quantitative analysis of the morphological bone changes was performed on decalcified and undecalcified bone using integrating filters and the point count principle An increased amount of unmineralized bone was found in 32 (53%) of the epileptics The trabecular osteoclastic resorption surfaces and the mean volume of periosteocytic lacunae were increased in 36 (69%) and 45 (75%) patients, respectively The calcification rate was decreased in relation to what is referred to elsewhere as normal The bone changes suggest a mineralization defect analogous to osteomalacia with secondary hyperparathyroidism An increased osteoid volume or thickness and decreased calcification rate were correlated to low dietary vitamin D intake low exposure to sunlight, high hepatic clearance rate of DPH combined drug treatment and the male sex These parameters should be considered risk factors of anticonvulsant osteomalacia

Recent investigations have demonstrated an increased frequency of hypocalcemia and elevated serum alkaline phosphatase values including both bone and liver isoenzymes in patients receiving chronic anticonvulsant therapy (2 12 16 25) A number of authors have reported radiological signs of bone disease (6 17 18 26 28) and a reduced bone mineral content measured by photone absorptiometry in both adults (2) and children (12)

The bone histology in patients receiving chronic anticonvulsant therapy has been described in a few severe cases (6 8) Changes analogous to osteomalacia have been found The literature contains no information on the frequency and degree of bone changes in larger groups of epileptic patients The frequency of biochemical and radiological evidence of osteomalacia in normal active adult epileptic out patients remains controversial as does the influence of various risk factors The purpose of the present study was to use morphometric analysis of undecalcified and decalcified bone to elucidate these problems

PATIENTS AND METHODS

The investigation comprised 60 randomly selected epileptic out patients 30 men aged 18–50 years (mean 27) and 30 women aged 18–47 years (mean 26) All fulfilled the following criteria the anticonvulsant therapy had lasted for more than 10 years all patients received diphenylhydantoin (DPH) some of them in combination with primidone carbamazepine phenobarbitone or ethosuximide all had a normal serum creatinine value none had symptoms of digestive or endocrine disease none received any medication apart from anticonvulsant drugs and all had a normal range of physical activity

Two groups of control subjects were investigated *Group I* totalled 16 subjects 8 men and 8 women with the same age distribution as the epileptic patients who had died suddenly in an accident or of coronary occlusion No sign of other disease was found at autopsy This group served as a reference group for the morphometric bone changes *Group II* comprised 60 persons 30 men and 30 women with exactly the same age distribution as the epileptic patients There were no significant differences between the two groups concerning height weight or serum creatinine None had symptoms of digestive or

Table I *Differences in biochemical parameters (mean ±S E) in epileptic patients and controls*

	N	S-calcium (mg/100 ml)	S phosphate (mg/100 ml)	S alkaline phosphatase (U/l)	U-calcium (mg/g creatinine)	U phosphate (mg/g creatinine)
Total						
Controls	60	9 71±0 03	3 87±0 07	147± 4	152± 7	539±17
Epileptics	60	9 61±0 03	3 90±0 06	203± 9	110± 6	532±19
p		<0 01	n s	<0 01	<0 01	n s
Males						
Controls	30	9 84±0 04 *	3 77±0 09	162± 6**	146± 6	542±27
Epileptics	30	9 71±0 05**	3 84±0 09	219±14*	106± 7	534±22
p		<0 05	n s	<0 01	<0 01	n s
Females						
Controls	30	9 58±0 04**	3 97±0 10	134± 5**	158±12	535±22
Epileptics	30	9 51±0 04*	3 95±0 09	188±10*	114± 9	530±30
p		n s	n s	<0 01	<0 01	n s

* $p<0\ 05$ ** $p<0\ 01$ Differences between sexes

endocrine disease or received any medication This group served as a reference group for biochemical parameters

After double labelling with 400 mg chlortetracycline given i m at a 14-day interval two bone biopsies were performed in the epileptic patients from the right ilium 2 cm behind the anterior superior iliac spine and 2 cm below the summit of the iliac crest In control group I the same specimen was obtained at autopsy by sawing Using the Zeiss integrating filter I and II and the point count principle the following five parameters were measured on undecalcified sections 6–8 μm thick embedded in methyl methacrylate (*a*) *absolute volume of trabecular bone* (AVTB) as the percentage of the sections occupied by trabecular bone (5 22) (*b*) *osteoid surfaces* (OS) as the percentage of osteoid-covered surfaces of trabecular bone (22) (*c*) *relative osteoid volume* (OV) as the percentage of lar bone area occupied by osteoid (5) (*d*) *index of* (OI) as the equation (OV/OS)×100 reflecting mean thickness of the osteoid border (Meunier personal communication) and (*e*) *trabecular osteoclastic resorption surfaces* (RS) as the percentage of trabecular bone surfaces occupied by a resorption lacuna (5) *Mean volume of periosteocytic lacunae* (μm^3) (POL) was measured on decalcified sections 4 μm thick as the mean of the product of length and width of 50 randomly selected lacunae (23) *Calcification rate (μm/day)* (CR) was measured on undecalcified sections 20 μm thick using ultra violet light as the mean distance between the middle of the fluorescent tetracycline lines in all double labelled zones (7)

For each patient a detailed history of the intake of vitamin D and calcium-containing foods and vitamin supplements throughout the year was obtained by a single investigator following a standard questionnaire The individual daily intake of vitamin D and calcium was calculated using tables of the composition of Danish foods (15)

Table II *Differences in bone morphometry (mean ±S E) in epileptic patients and controls*

	N	AVTB (%)	OS (%)	OV (%)	OI	CR (μm/d)	RS (%)	POL (μm^3)
Total								
Controls	16	22 9±1 0	9 2±1 4	1 5±0 3	15 9±1 5		3 3±0 1	52 0±1 0
Epileptics	60	23 4±0 6	14 9±1 0	4 1±0 3	28 5±1 2	0 73±0 02	5 0±0 2	71 6±0 9
p		n s	<0 01	<0 01	<0 01		<0 01	<0 01
Males								
Controls	8	21 8±1 1	6 5±1 4	1 3±0 3	18 4±1 3		3 4±0 1	52 7±1 9
Epileptics	30	23 4±0 9	16 6±1 4	4 6±0 4*	29 0±1 9	0 72±0 03	5 3±0 3	72 3±1 7
p		n s	<0 01	<0 01	<0 01		<0 01	<0 01
Females								
Controls	8	23 9±1 8	11 9±2 3	1 8±0 5	13 4±2 7		3 1±0 3	51 3±0 8
Epileptics	30	23 6±0 9	13 3±1 5	3 5±0 3*	27 9±1 5	0 74±0 02	4 7±0 3	70 8±1 7
p		n s	n s	<0 01	<0 01		<0 01	<0 01

* $p<0\ 05$ Differences between sexes

Table III *Patients with abnormal biochemical or morphometric parameters (exceeding mean ±2 S D of the values in control group I)*
Differences between sexes determined by Fisher's exact test

	Total (N)	(%)	Males (N)	Females (N)	p
Hypocalcemia	4	7	2	2	n s
Elevated serum alkaline phosphatase	25	42	11	14	n s
Decreased urinary calcium excretion	11	18	11	0	<0 002
Increased OS	18	30	17	1	<0 002
Increased OV	32	53	25	7	<0 002
Increased OI	32	53	20	12	n s
Increased RS	36	60	23	13	<0 02
Increased POL	45	75	22	23	n s

An estimate of hours per day spent outdoors throughout the year was obtained for each patient Individual exposure to sunlight was calculated with information from the Danish State Meteorological Office on the average minutes of bright sunshine per day throughout the year at different geographical locations

From each patient and control in group II a fasting blood sample was obtained on three different days for determination of serum calcium serum phosphate serum alkaline phosphatase and serum creatinine The results were expressed as mean values and serum calcium was corrected for individual variation in serum protein concentration (24) A 24 hour excretion of calcium phosphate and creatinine was determined on a non-restricted diet The steady state concentration of DPH (31) phenobarbitone (20) and carbamazepine (3) in serum was determined in all patients 14–15 hours after the last ingestion of anticonvulsants The individual clearance rate of DPH was calculated from the equation

$$Cl_{DPH} = \frac{D_{DPH}}{C_{DPH}}$$

where C_{DPH} is the steady state concentration of DPH and D_{DPH} the daily dose of DPH

Statistical significance of differences in group means was determined by the Wilcoxon test for two samples and correlation coefficients by Spearman s rank correlation Differences in frequencies were determined by Fisher's exact test

RESULTS

Population study

Biochemical changes (Table I) In the epileptic patients there was a significant decrease in serum calcium and in the urinary excretion of calcium The serum alkaline phosphatase was increased No significant alteration in serum phosphate or urinary phosphate excretion was found Table III gives the frequency of abnormal biochemical findings

Bone changes (Table II) There was no significant difference in the AVTB between patients and controls In the epileptics the percentage of OS was significantly increased as were the OV and OI The CR was decreased compared with the mean value of 1 2 μm/day reported by Frost (7) A significant increase was found in the RS and in the POL The frequency of abnormal morphometric values is given in Table III In none of the patients were all the parameters within the normal range (mean ±2 S D *from control group I)*

Sex and age Both in the epileptics and in control group II serum calcium and serum alkaline phosphatase were significantly higher in males than in females (Table I) In the epileptic patients the decrease in serum calcium was significant only in the males There was no difference between the sexes in the frequency of hypocalcemia or elevated serum alkaline phosphatase values Reduced urinary excretion of calcium was found in 11 male and 0 female epileptics (Table III) This difference in frequency is significant The percentage of OS and the OV were higher in the male epileptics than in *the females (Table II) These differences were not* found in the control group The increase in OS was significant only in the male epileptics A significantly higher frequency of increased OS OV and RS was found in the male epileptics (Table III) There was no correlation between age and biochemical or morphometric parameters

Risk factors

Low dietary vitamin D The mean daily ingestion of vitamin D was for males 282±37 IU (range 45–860) and for females 292±40 IU (range 35–980) Table IV gives the results of the morphometric analysis of *bone changes in patients with a daily ingestion of* vitamin D of above or below 250 IU respectively There were no quantitative differences in the AVTB OI RS or POL Among all the epileptics highly significant increases were noted in the percentage of OS and the OV and a highly significant decrease in the CR in the group with a low vitamin D intake compared with the high intake group These differences were significant at a lower level or not significant in males and females (Table IV) There was a significant correlation between the daily intake of vitamin D and the percentage of OS

Table IV *Influence of dietary vitamin D on bone morphometry (mean±S E) in epileptic patients receiving anticonvulsant drugs*

Vitamin D (IU/d)	N	AVTB (%)	OS (%)	OV (%)	OI	CR (μm/d)	RS (%)	POL (μm²)
Total								
>250	31	23 5±0 9	12 0±0 9	3 3±0 3	28 4±1 4	0 79±0 02	5 1±0 3	72 2±1 8
≤250	29	23 4±0 8	18 1±1 8	4 8±0 4	28 5±1 9	0 66±0 03	4 8±0 3	71 1±1 6
p		n s	<0 01	<0 01	n s	<0 01	n s	n s
Males								
>250	15	22 9±1 1	14 1±1 1	4 0±0 3	28 5±1 9	0 80±0 03	5 4±0 4	74 3±2 0
≤250	15	23 9±1 5	19 2±2 5	5 3±0 7	29 5±3 4	0 64±0 05	5 2±0 5	70 3±2 9
p		n s	n s	n s	n s	<0 02	n s	n s
Females								
>250	16	24 1±1 5	10 1±1 1	2 7±0 3	28 2±2 2	0 77±0 03	4 9±0 5	70 0±2 9
≤250	14	22 9±0 8	17 0±2 7	4 4±0 5	27 6±2 0	0 68±0 04	4 6±0 3	71 8±1 6
p		n s	<0 02	<0 05	n s	n s	n s	n s

($R=-0$ 30 $p<0$ 05) the OV ($R=-0$ 38 $p<0$ 01) and the CR ($R=0$ 40 $p<0$ 02)

Low exposure to sunlight The mean daily exposure to sunlight was for males 56±6 min (range 14–169) and for females 42±4 min (range 7–119) The patients were divided into two groups with regard to exposure to sunlight of above or below 45 min/day Among all the epileptics the OI was significantly increased ($p<0$ 05) in the low-exposure group (30 0±1 7) compared with the high-exposure group (26 7±1 6) Among the females a significant reduction ($p<0$ 02) in CR was found in the low group (0 68±0 04 against 0 78±0 02)

Low dietary calcium The mean daily intake of calcium was for males 1 200±90 mg (range 450–2 400) and for females 960±80 mg (range 150–1 800) There was no correlation between dietary calcium and morphological bone changes

Hepatic clearance of DPH The mean clearance rate was for males 35±4 ml/min (range 10–104) and for females 48±9 ml/min (range 10–208) Table V gives the results of the morphometric analysis of bone changes in two groups of patients with clearance rates above and below 30 ml/min respectively Among all the epileptics the group with a high clearance rate had a significantly higher percentage

Table V *Influence of hepatic clearance rate of DPH on bone morphometry (mean±S E) in epileptic patients receiving anticonvulsant drugs*

DPH clearance (ml/min)	N	AVTB (%)	OS (%)	OV (%)	OI	CR (μm/d)	RS (%)	POL (μm²)
Total								
>30	30	23 4±0 8	17 0±1 7	4 9±0 4	30 9±1 7	0 65±0 03	4 8±0 4	74 5±1 7
≤30	30	23 5±0 9	12 7±1 0	3 2±0 3	26 1±1 5	0 79±0 02	5 0±0 3	68 4±1 4
p		n s	<0 02	<0 01	<0 01	<0 01	n s	<0 01
Males								
>30	14	24 4±1 4	20 3±2 2	5 9±0 5	31 4±2 6	0 63±0 06	5 6±0 5	75 7±2 3
≤30	16	22 5±1 2	13 1±1 3	3 4±0 4	26 9±2 5	0 78±0 03	5 1±0 4	69 3±2 [illegible]
p		n s	<0 02	<0 01	n s	<0 05	n s	<0 05
Females								
>30	16	22 6±1 0	14 1±2 7	4 0±0 5	30 4±2 3	0 67±0 03	4 5±0 4	73 4±2 4
≤30	14	24 7±1 5	12 2±1 7	3 0±0 4	25 2±1 6	0 80±0 03	4 8±0 4	67 4±1 7
p		n s	n s	n s	n s	<0 01	n s	n s

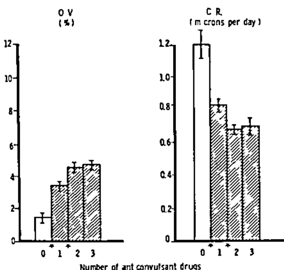


Fig 1 Correlation between number of drugs prescribed to epileptic patients and relative osteoid volume (*O V*) and calcification rate (*C R*) The normal value of relative osteoid volume is derived from our own control group The normal mean value of calcification rate is reported by Frost (7) ▨=epileptics □=controls $^*p<0.05$

of OS OV OI and POL The CR was significantly reduced These differences were significant at a lower level or not significant in the subgroups of males and females (Table V) There was a significant correlation between the clearance rate of DPH and the OV ($R=0.31$ $p<0.02$) the OI ($R=0.29$ $p<0.05$) the CR ($R=-0.43$ $p<0.01$) and the POL ($R=0.32$ $p<0.02$)

Number and kind of anticonvulsant drugs Fifteen patients received one anticonvulsant drug (DPH) 31 two drugs and 14 three drugs or more In all three groups the OS OV OI RS and POL differed significantly from the values of control group I The OV increased and the CR decreased with an increasing number of anticonvulsant drugs prescribed (Fig 1) These differences were significant ($p<0.05$) between the single drug and the combined drug groups but not between the two drug and the three-or more drug groups

The four most common anticonvulsant drug regimes were DPH (15 patients) DPH+primidione (14 patients) DPH+carbamazepine (13 patients) and DPH+primidione+carbamazepine (9 patients) The CR was significantly lower ($p<0.05$) in patients receiving DPH+carbamazepine and the OV higher ($p<0.05$) in patients receiving DPH+primidione than in those receiving DPH only

Duration of therapy and serum concentrations of anticonvulsants There was no correlation between these parameters and the morphological bone changes

DISCUSSION

Our studies of bone changes in epileptic patients treated with anticonvulsants for more than 10 years indicate a mineralization defect analogous to osteomalacia with an increased amount of osteoid and a decreased calcification rate The diagnosis is confirmed by a decrease in serum calcium concentration and urinary calcium excretion together with an increase in serum alkaline phosphatase values The reduced level of 25 OH calciferol reported by several authors (11 12 29) and the therapeutic effect of vitamin D on bone lesions (2 17 26) are in agreement with our findings The increase in trabecular osteoclastic resorption surfaces and mean volume of periosteocytic lacunae suggests a secondary hyperparathyroidism Elevation of serum immunoreactive parathormone level with subsequent reversion after therapeutic administration of vitamin D or i v calcium infusion has been reported in patients with drug induced osteomalacia (8 9)

In our population of adult epileptic out patients 53% had increased relative osteoid volume 60% increased resorption surfaces and 75% increased periosteocytic lacunae This incidence of bone disease is surprisingly high compared with reports elsewhere In a similar population of 226 Danish out patients with epilepsy only 18% had a bone mineral content below the normal range (mean ±2 S D) (2) measured by photon absorptiometry Radiological evidence of bone disease was found in 15% of a German juvenile epileptic out patient population (17) and a study in the USA did not reveal any case of osteomalacia in routine skull X ray of 15000 juvenile epileptic out patients (19) Radiological changes in the trabecular pattern of the proximal end of the femur were found in 77% of adult epileptic patients compared with 24% of control patients (28) There may be several explanations of these differences in incidence of bone disease

From our study as well as from others it appears that reduced daily intake of vitamin D and reduced exposure to sunlight are important risk factors Variations in these factors among different populations could probably explain the differences in the ob-

served incidence of osteomalacia The daily intake of vitamin D in the present population was not lower than the average of about 200 IU from food substances in the Danish population (14) The patients were ambulatory with normal opportunities for exposure to sunlight but it is of interest that the current study was conducted during the winter when exposure to sunlight would be at a minimum However the fact that only four of the patients (7%) were hypocalcemic indicates that the degree of osteomalacia in our material was not pronounced Previous reports on epileptics have shown incidences of hypocalcemia of 23% and 30% for in patients (16 25) and 12% and 19% for out patients (2 11) A reasonable explanation of the high frequency of observed bone disease in our population is that the morphological analysis of bone changes is a more sensitive diagnostic procedure

From the present study it appears that reduced daily intake of vitamin D and reduced exposure to sunlight involve a risk of anticonvulsant osteomalacia This is in agreement with the finding that serum 25 OH-calciferol concentration showed a positive correlation with the dietary intake of vitamin D in both epileptic patients and normal controls being lower in the drug treated group at any level of vitamin D intake (12) In institutionalized mentally retarded children receiving anticonvulsants evidence of rickets was found only in non ambulatory patients who stay indoors (18) and in patients at a residential centre hypocalcemia was found in 25% working indoors compared with 8% working outdoors (25) Furthermore a group of healthy persons showed a seasonal variation in serum 25 OH calciferol concentration with a maximum in the late summer and early autumn (21)

The administration of hepatic microsomal enzyme inducing drugs results in an increased rate of conversion of vitamin D_3 to more polar compounds including 25 OH-cholecalciferol and an increased excretion of vitamin D metabolites in the bile (10 27) These findings suggest that the degree of hepatic induction is of decisive importance for the incidence and severity of osteomalacia We have calculated the individual hepatic clearance rate of DPH in an attempt to elucidate this problem finding that it might be a measure of the degree of induction for the following reasons (*a*) the initial process in the metabolism of DPH is a hydroxylation to 5-phenyl 5-(paraphenyl)-hydantoin by hepatic microsomal enzymes (1) It is then coupled mainly to glucuronic acid and ultimately eliminated by the kidney Both hydroxylation and glucuronidation are known to be enhanced by induction (4) (*b*) the metabolism of DPH is in fact accelerated by giving another inducing drug e g phenobarbitone (4) or carbamazepine (13) (*c*) in the present study we found that the clearance rate of DPH correlated inversely with serum bilirubin ($R=-0.30$ $p<0.05$ unpublished) which is in agreement with the finding that induction with phenobarbitone enhances the hepatic uptake and excretion of bilirubin (30) The present investigation has shown that a high degree of induction expressed in a high clearance rate of DPH is correlated with the degree of osteomalacia (high relative osteoid volume and low calcification rate) and the degree of secondary hyperparathyroidism (increased mean volume of periosteocytic lacunae)

Several studies have shown a correlation between the number of drugs prescribed and serum calcium (12 25) serum alkaline phosphatase serum 25 OH-calciferol bone mineral content (12) and radiological alterations in the proximal end of the femur (28) In our study the degree of osteomalacia was more pronounced in patients receiving combined drug therapy than in those on a single drug Our results showing that the calcification rate decreased and the relative osteoid volume increased with the number of drugs prescribed further emphasize that combined-drug therapy is a risk factor The effect of combined drug therapy might be explained by a higher degree of hepatic induction In the present study the mean clearance rate of DPH was higher in patients on a combined drug regime but the difference was not significant

No correlation was found between the duration of therapy and the morphological bone changes This is in agreement with some authors (12 28) and in disagreement with others (2 17) The lack of correlation could be due to the fact that all patients had received anticonvulsants for more than 10 years It is noteworthy that no reduction in the absolute volume of trabecular bone was found after 10–35 years of anticonvulsant therapy

We have no explanation for the higher frequency of decreased urinary excretion of calcium increased osteoid surfaces increased osteoid volume and increased osteoclastic resorption surfaces in the male epileptics There were no differences between the sexes concerning daily vitamin D intake

exposure to sunlight hepatic clearance rate of DPH or number of prescribed drugs which could explain the higher frequency of osteomalacia in the male epileptics

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Serum Lipids in Alcoholics

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ABSTRACT Fasting serum lipid values (cholesterol, triglycerides and phospholipids) have been analysed in a group of 85 male and 10 female alcoholics of various ages in connection with an acute drinking bout and compared to the values of twice as many control subjects The most prominent finding was an increase in the mean concentration of triglycerides and phospholipids, most marked in the younger age groups The elevations, however, were moderate and most alcoholics had the same serum lipid values as the controls Serum triglyceride values above 2 and 3 mmol/l, respectively, occurred in 23% and 4% in controls and in 28% and 13% in alcoholics It is suggested that excessive intake of alcohol induces hypertriglyceridaemia only when other factors are present One such factor may be a reduced i v fat tolerance

Hyperlipidaemia of type IV and type V according to the nomenclature of Fredrickson et al (11) is characterized by elevated levels of serum triglycerides but usually normal concentrations of serum cholesterol unless there is very marked elevation of triglycerides when there is also a concomitant rise in cholesterol The major difference between the more common type IV and type V is the presence in the latter of chylomicrons in fasting serum samples In Stockholm hypertriglyceridaemia is common in patients with coronary heart disease (5) and it is also a risk factor for the development of future coronary heart disease (6) Furthermore apparently healthy men with various forms of hypertriglyceridaemia—hyperlipoproteinaemias types II B III and IV according to the WHO nomenclature (1)—have an increased frequency of ischaemic exercise ECGs (7) Elucidation of the etiology and pathogenesis of hypertriglyceridaemia is thus an important task considering the high and increasing frequency of coronary heart disease

Several factors have been recognized to be closely associated with hypertriglyceridaemia Among these are diabetes and glucose intolerance obesity dietary carbohydrates plasma free fatty acids and alcohol In 1958 Zieve (15) reported the occurrence of hyperlipidaemia jaundice and mild haemolysis in 20 alcoholics after prolonged periods of heavy drinking In a survey of 211 consecutive patients seen at Hammersmith Hospital Chait et al (10) found that alcohol next to diabetes was the most common cause of secondary hyperlipidaemia followed by renal diseases Furthermore in a recent population study on 202 apparently healthy men (14) the stated frequency of alcohol ingestion was significantly and positively related to serum triglyceride concentration ($p<0.01$)

It is always difficult to assess the intake of alcohol and it is thus not easy to evaluate the frequency with which alcohol may be a causative factor in hypertriglyceridaemia In an attempt to circumvent this problem in the evaluation of the role of alcohol in hypertriglyceridaemia we have looked at the problem from the opposite angle and studied the frequency of hypertriglyceridaemia in alcoholics

MATERIAL

Patients admitted to the special ward for treatment of alcoholics Beckomberga Psychiatric Hospital Stockholm during March 1–May 30 1971 have included altogether 85 men and 10 women These patients are chronic alcoholics generally admitted after an acute drinking bout

For each patient two sex and age matched controls have been chosen from the clientele attending a health

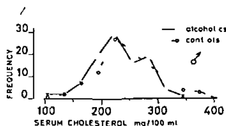


Fig 1 Frequency distribution of serum cholesterol values for male alcoholics and controls

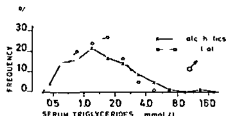


Fig 2 Frequency distribution of serum triglyceride values for male alcoholics and controls

alcoholics than in the controls in all age groups Statistical difference is found only in the age group 51–60 ($p<0\ 01$)

Serum triglyceride values were elevated in the younger *male* groups of alcoholics—statistically significant in 21–50-year old men at the 0 1% level Above the age of 50 the triglyceride levels in alcoholics were similar to those of the controls

Serum phospholipids total lipid P lecithin as well as lysolecithin showed the same pattern as triglycerides with higher values in the younger male age groups of alcoholics than in the controls Statistically significant differences are found in the age groups 21–50 for total lipid P ($p<0\ 001$) and lecithin ($p<0\ 001$) and in the age groups 21–40 for lysolecithin ($p<0\ 01$)

While there were differences between male alcoholics and controls *female* alcoholics did not differ significantly from their controls with regard to serum concentrations of cholesterol triglycerides and phospholipids

The frequency distribution of cholesterol for men (Fig 1) shows that with regard to cholesterol the main difference between controls and alcoholics is the higher frequency of values above 300 mg/100 ml in control persons

The *frequency distribution of serum triglycerides* (Fig 2) showed an opposite pattern than that of cholesterol with a higher frequency of high values for the alcoholics The frequency of serum triglyceride values above 3 mmol/l was 12 7% in alcoholic men compared to 4 3 in controls ($p<0\ 05$ Table III) Particularly alcoholics aged 31–40 had the highest frequency of high serum triglyceride values

A battery of liver function tests is available for 79 of the alcoholic men Table IV gives the mean values and ranges for these variables Although serum bilirubin values on an average are within normal limits 45–50% of the patients had elevated SGOT and/or SGPT values as well as elevated ESR (28%) and elevated serum iron values (62%) Serum amylase values were normal in 90% of the subjects Total serum protein and serum albumin were normal in 93% of the alcoholics

An attempt has been made to study whether serum lipid values differ between patients with normal and those with pathologic liver values No complete liver function studies with e g bromsulphalein retention tests were performed Attempts to correlate serum lipid values with signs of more acute liver damage e g serum transaminase values or chronic hepatic disease as e g alkaline phosphatases were unsuccessful The material was then divided into two groups one consisting of patients considered to have definite pathologic liver function ($n=40$) (3 or more of the following tests pathologic ESR serum bilirubin SGOT SGPT SLDH and serum alkaline phosphatases) the other of patients without such signs ($n=39$) The mean age was the same in both groups (47 and 44 years respectively) The results for the whole groups are shown in Table V Alcoholics with pathologic liver function did not differ significantly from those with normal liver function with regard to their lipid values

Table III *Frequency of serum triglyceride values above 3 0 mmol/l in males*

	Age group						
	21–30	31–40	41–50	51–60	61–70	71–	Total
Alcoholics							
n	9	19	26	16	13	2	85
%	–	21	14	13	8	–	12 7
Controls							
n	18	38	52	32	23	1	164
%	–	–	6	13	–	–	4 3

The difference between the frequencies is significant at the 5% level (χ^2 test)

Table IV *Liver values in alcoholics*

	Laboratory normal value	Patient values		Percentage of patients with pathologic value
		Mean	Range	
ESR (mm/h)	<12	14	2–108	28
Serum iron (μg/100 ml)	*80–160*	*171*	*30–308*	62
Serum TIBC (μg/100 ml)	250–400	317	183–435	13
Serum bilirubin (mg/100 ml)	<1 0	0 9	0 3–1 7	34
SGOT (U/ml)	<40	67	15–322	49
SGPT (U/ml)	<35	52	11–253	45
SLDH (U/ml)	<300	254	130–540	17
Serum alkaline phosphatase (U/ml)	<6	4 6	2 3–8 9	15
Serum Mg (mEq/l)	1 4–1 9	1 55	1 15–2 20	16
Serum amylase (U/ml)	85–300	168	62–337	9
Total protein (g/100 ml)	6 0–8 0	6 8	5 3–8 2	7
Albumin (g/100 ml)	3 5–5 0	4 1	2 5–5 1	7

DISCUSSION

Our results show that on an average the alcoholics had higher serum triglyceride and phospholipid values but that the cholesterol values tended to be lower The changes were most marked in the younger alcoholics (25–45 years) The frequency of high serum triglyceride values arbitrarily defined as 3 mmol/l or more was 4 3% in controls and 12 7% in the alcoholics The difference is still more striking if we look at the ages 30–50 years where the incidence of high triglyceride values was 17% in alcoholics and 3 3% in controls Athough it was not possible for technical reasons to type the hyperlipidaemias it is most likely that the prevailing type was type IV—as the hyperlipidaemia was characterized by moderately high serum triglyceride and low or normal cholesterol values Hyperlipoproteinaemia type V was probably present in only one of the alcoholics whose serum triglyceride level was around 15 mmol/l

One purpose of this work was to obtain an idea of the frequency of hypertriglyceridaemia in severe alcoholics An upper limit of normal triglyceride value for males is probably around 2–2 5 mmol/l (4 8) If we use e g the lower limit however, 23% of the controls and 28% of the alcoholics had hyperlipidaemia It thus appears likely that excessive alcoholism predisposes to more major hyperlipidaemia with triglyceride concentrations above 3 mmol/l The frequencies of triglyceride values above 3 mmol/l were 4% of controls and 13% for alcoholics It is quite important to note that the *majority of alcoholics had triglycerides within normal limits* This thus suggests that it is not only the excessive intake of alcohol which induces alcoholic hypertriglyceridaemia but that additional factors operate One such factor may be the presence of a defective system for the clearance of plasma triglycerides Indeed Chait et al (10) have shown that the i v fat tolerance with Intralipid® (9) is substantially reduced in patients with alcoholic hypertriglyceridaemia both when these patients are hyperlipidaemic (on alcohol) and normolipidaemic (off alcohol) We suggest that alcohol induces

Table V *Serum lipid values in alcoholics with pathologic and normal liver functions and in controls (mean ±S E M)*

	Pathologic liver function	Normal liver function	All alcoholics	Controls
n	40	39	85	164
Age (y)	46 8±2 0	44 4±2 0	46 2±1 4	45 5±1 1
Cholesterol (mg/100 ml)	239±7 7	219±6 5	232±5 1	248±4 0
Triglycerides (mmol/l)	1 66±0 22	1 83±0 16	1 86±0 14	1 54±0 007
Phospholipids (μg/ml)	124±3 6	112±2 9	105±2 4	105±2 1

hyperlipidaemia only in subjects who have a reduced i v fat tolerance and thus are sensitive to all measures which may increase plasma triglyceride production

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Cutaneous Reactions to Propranolol (Inderal®)

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ABSTRACT Six patients with psoriasiform cutaneous eruptions that developed during long term therapy with propranolol (Inderal®) have been studied The cutaneous changes closely resembled those seen during treatment with practolol (Eraldin®) The duration of treatment before the rash was recognized averaged 10 months, which is about the same latency period as in patients with practolol induced exanthemas The exanthemas disappeared gradually within 1–5 weeks after treatment with propranolol had been stopped In 4 of 5 patients the skin eruptions reappeared within 2–4 days after oral challenge with propranolol In the fifth patient, who developed a rash after challenge with practolol and severe abdominal colics after challenge with oxprenolol no further provocation tests with propranolol were attempted Skin biopsies obtained from 3 patients showed a microscopical picture similar to that seen in practolol exanthemas The pathogenetic mechanism responsible for these adverse cutaneous reactions is unknown However, since the possibility exists that these changes may be caused by blockade of the epidermal β receptors it is recommended that all patients receiving β blocking drugs should be examined carefully for similar adverse reactions Special attention should be drawn to the reversible skin changes since during treatment with practolol these have often preceded serious complications from other organs

It is now well recognized that practolol may cause several adverse reactions including various cutaneous eruptions and ocular reactions (5 7 8 9 10 13 14) sclerosing peritonitis (2) LE syndrome (11) and nephrotic syndrome (4)

If as we have previously suggested (8) β blockade per se is a major factor in the development of these reactions one might expect to find similar symptoms in patients on long term treatment with other β blocking agents including propranolol Only a few cases of skin reactions to other β blockers have been reported (3 6 8)

During the past few months we have therefore looked carefully for these symptoms and in the present communication we present six patients who developed cutaneous symptoms including evidence of keratoconjunctivitis sicca during treatment with propranolol The symptoms closely resembled those occurring after practolol and they disappeared shortly after discontinuation of therapy and reappeared in response to renewed exposure to the drug

MATERIAL

Six patients were studied Their ages ranged from 49 to 75 years Propranolol was used in dosages of 40–400 mg daily for treatment of hypertension in three for angina pectoris in two and for arrythmias in one (Table I) With the exception of case 5 the average duration of treatment was 10 months till appearance of the cutaneous manifestations One patient (no 3) received concomitant treatment with thiazide and hydralazine 100 mg daily another (no 4) triamteren and bumetanide and a third (no 6) furosemide and digoxin The treatment of the other three patients consisted of propranolol only With the exception of case 5 who was originally referred to us because of a practolol induced exanthema none of the patients had suffered from previous skin disorders and none had cases of psoriasis in the family

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Table I *Clinical data on the patients*

Case no	Sex	Age (y)	Indication for propranolol	Propranolol dosage (mg/d)	Duration of treatment at appearance of exanthema (mo)	Nail changes
1	♂	68	Hypertension	80	12	No
2	♀	49	Hypertension	160	10	Yes
3	♂	54	Hypertension	400	18	Yes
4	♂	63	Angina pectoris	40	6	Yes
5	♀	65	Angina pectoris	120	3 d	No
6	♂	75	Extrasystoles	120	3	Yes

RESULTS

Clinical manifestations

Five patients developed a psoriasiform slightly itchy cutaneous eruption characterized by dry erythematous scaly nummular lesions on the extensor surfaces of the extremities and torso as well as the scalp (Figs 1 and 2) Patient 6 developed exfoliative dermatitis In four patients pronounced hyperkeratosis was present on the palms and soles (Fig 3) Nail changes presenting as pitting thickening and discolouration were seen in four of the patients (Fig 4) and in one tiny pustules surrounded the nails One patient complained of eye dryness and pain No keratoconjunctivitis sicca was demonstrated using Schirmer s test No corneal lesions were detectable

No other side effects including sclerosing peritonitis otitis etc were recorded No antinuclear or or LE cells were demonstrated Routine tests were normal

When treatment with propranolol was stopped the cutaneous manifestations disappeared within one to five weeks

Oral challenge tests

Five patients volunteered to have an oral challenge test performed one (no 4) suffering from hepatitis was not tested The etiology of this hepatitis remained unexplained despite intensive studies in the Department of Hepatology This patient was not reexposed to propranolol since this drug could not be completely ruled out as the cause of the hepatitis although this type of side effect has not been reported previously

The tests were performed 1–5 weeks later after the initial skin lesions had cleared Propranolol in the dosage previously used by the patient was given for five days When the skin eruptions following the test had cleared subsequent tests were performed using practolol alprenolol oxprenolol and pindo



Fig 1 Slight diffuse scaling and a psoriasis like plaque on the scalp

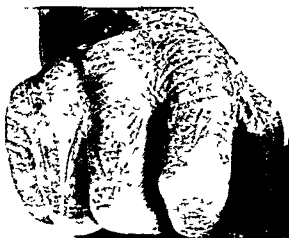


Fig 2 Hyperkeratotic scaly lesion on the hand and the fingers



Fig 3 Hyperkeratotic psoriasiform changes on the soles

lol The results are summarized in Table II In four patients the skin eruptions reappeared within three days after propranolol In one patient (no 2) no reaction occurred within five days after readministration of propranolol This patient however developed a skin eruption similar to his initial propranolol induced exanthema when she was tested subsequently with practolol Furthermore when later on oxprenolol was administered this had to be discontinued because of severe abdominal colics In another patient (no 1) treatment with alprenolol was tried but had to be stopped after six days because of reappearance of the skin rash

One patient (no 5) was reexposed twice to propranolol and on both occasions she developed a papular scaly psoriasiform rash as well as irritation itch and dryness of the conjunctivae This patient is of particular interest since she had initially suffered from a practolol induced rash

Intracutaneous tests with propranolol were not performed since even concentrations as low as 0 5–5% W/W in saline caused a severe local irritant reaction

Histology

Skin biopsies from psoriasiform cutaneous lesions were obtained in three patients (nos 1 3 and 6) The histological pictures were similar with slight epidermal hyperplasia acanthosis patchy parakeratosis and oedema of the epidermis Several polymorphonuclear leucocytes were present in the epidermis occasionally forming Munroe like microabscesses (Fig 5) In the upper part of the dermis a moderate infiltrate of mononuclear cells was present mainly located perivascularly The dermal papillae were elongated with dilated capillaries Thus the histological picture to some degree had features resembling those seen in early psoriatic lesions



Fig 4 Psoriasis like nail changes with thickening discolouration subungual hyperkeratosis and pitting

Table II *Exposure to various β-blocking drugs*

	Duration of treatment until appearance of cutaneous reactions				
Case no	Propranolol (40–400 mg/d)	Practolol (300 mg/d)	Alprenolol (300 mg/d)	Oxprenolol (120 mg/d)	Pindolol (15 mg/d)
1	3 days	n d	6 days	n d	n d
2	Negative	5 days	Negative	3 days[a]	n d
3	4 days	n d	n d	n d	n d
5	3 days	3 days	2 days[b]	2 days[b]	2 days[b]
6	2 days	n d	n d	n d	n d

n d =test note done [a] Abdominal colics but no exanthema [b] Itch though no rash

DISCUSSION

The results of the present study indicate that propranolol may induce adverse cutaneous reactions similar to those seen after treatment with practolol Practolol exanthemas may present many clinically different pictures They may be psoriasiform (5 9) lichenoid (5) maculo papular or have an LE like appearance The skin lesions in our six patients on propranolol were all of the psoriasiform type Cutaneous side effects due to propranolol are probably rare Although the drug has been extensively used for more than ten years only one case with cutaneous manifestations similar to those in our patients has been published earlier (10) It is therefore noteworthy that we found six patients within a few months This may indicate that previously the etiology of similar rashes in other patients has escaped attention The rare occurrence of adverse cutaneous side effects due to propranolol compared with those seen after practolol might be explained by differences in affinity to the epidermal β receptors and/or the differences in the metabolization of the two drugs (1)

The diagnoses in our patients were supported by the clinical observations The cutaneous manifestations closely resembled those seen during treatment with practolol (5 14) and even the histological picture obtained in three of these patients was similar to that previously described in psoriasiform practolol exanthema (9) The duration of treatment with propranolol before the rash was recognized averaged 10 months which is about the same latency period as in patients with practolol exanthema (5) Furthermore reexposure to propranolol caused the cutaneous manifestations to reappear in four of five patients tested In one of the five patients (no 2) extension of the reexposure beyond five days might have yielded a positive result but the test could not be repeated since we feared abdominal complications after the patient had reacted with severe abdominal pains following exposure to oxprenolol

The pathogenic mechanisms responsible for



Fig 5 Light micrograph from a psoriasiform cutaneous lesion showing epidermal hyperplasia acanthosis hyper and parakeratosis The dermal papillae are elongated with dilated capillaries and an infiltrate of mononuclear cells is seen mainly located perivascularly

these exanthemas are unknown Immunological mechanisms have been suggested to explain the cutaneous eruptions seen in patients treated with practolol but so far the evidence which included various cutaneous tests has failed to support the view that a type I or type IV reaction could be held responsible (5 8)

As a working hypothesis we have previously suggested that blockade of the epidermal β receptors might lead to a decreased intracellular concentration of cyclic AMP (8 9) In the rapidly dividing cells of psoriatic epidermis cyclic AMP is low (12) This hypothesis might help to explain why abnormal proliferative dermatoses may occur after various β blocking agents including propranolol Work is currently in progress to elucidate this possibility

Since other β blocking agents including propranolol as we have shown may cause similar side effects to those described after practolol the clinician should still be alert to this possibility in patients during long term treatment with β blocking drugs

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Ventricular Fibrillation after Intravenous Atropine for Treatment of Sinus Bradycardia

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ABSTRACT A patient with acute myocardial infarction and sinus bradycardia has been treated with 0 5 mg atropine intravenously Shortly after the injection he showed a sinus tachycardia then developed ventricular ectopic beats, ventricular tachycardia and ventricular fibrillation which was treated successfully with electrical countershock

Bradyarrhythmias are a common feature in early myocardial infarction Incidences of 11–27% have been reported (1 4 8 11) These bradyarrhythmias have been considered to represent a potential danger because of hemodynamic and conduction disturbances and the use of vagolytic agents atropine or methylscopolamine i v has therefore been recommended However the benefit of atropine during bradycardia in acute myocardial infarctions (AMI) has been questioned recently by American experimental investigators (3 6) It is also well documented that i v atropine can actually precipitate serious ventricular arrhythmias (1 9 10 16) and increase the area of ischemia during myocardial infarction (14) Atropine might thus aggravate coronary ischemia and precipitate dangerous arrhythmias

This report deals with a patient who developed ventricular fibrillation after i v administration of 0 5 mg atropine

CASE REPORT

A 66-year-old man had had myocardial infarction in 1967 and 1971 For the past 2 years he had suffered from angina pectoris In Oct 1973 he was admitted to the CCU because of chest pain On admission ECG showed sinus rhythm 52 beats/min and evidence of acute diaphragmatic infarction BP was 110/70

Enzyme changes verified the diagnosis After 3 hours in hospital the ECG showed increasing bradycardia but at no time did premature ventricular beats develop Because of rates between 30 and 35 beats/min 0 5 mg atropine was given i v BP 105/75 He also received 6 5 mg thiethylperazine i v because of nausea

During the 12 min following the atropine injection there was a progressive acceleration of the sinus rhythm and at a rate of 70 beats/min the patient developed premature ventricular beats followed by ventricular tachycardia and then fibrillation After 50 mg Xylocaine i v defibrillation was achieved by electrical countershock (Fig 1)

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DISCUSSION

The ventricular fibrillation in this patient might be coincidental with the atropine injection but the following observations speak in favour of a causal relationship At no time during the bradycardia did premature ventricular beats develop The fibrillation appeared within 12 min after the administration of atropine and was preceded by frequent premature ventricular beats

The same observation has been reported by others (1 10 12 16) Norris et al (12) demonstrated recently in a clinical study that major ventricular arrhythmias did not usually occur at the time when bradycardia was present They also found that the hospital mortality among patients with sinus bradycardia (below 60) was significantly lower (6%) than among those with sinus tachycardia (over 100) (26%) This agrees with earlier reports (5 8) and tends to indicate that sinus bradycardia is associated with small infarctions and a low incidence of cardiac failure and rhythm disturbances and thus carries a good prognosis These observations sug

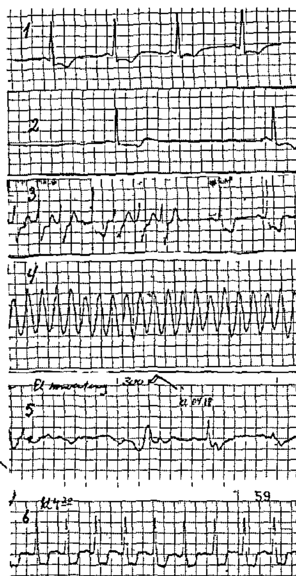


Fig 1 Monitor leads taken continuously *1* = the ECG on admission *2* = at the moment the patient received 0 5 mg atropine At a sinus rate of 70/min there are runs of ventricular beats which are followed by ventricular fibrillation Strip *5* shows the ECG just after the countershock 2 min later there is sinus rythm Paper speed 25 mm/sec

gest a benign course of sinus bradycardia during the hospital phase and a very recent work by Lie et al (9) seems to favour such a suggestion

Experimental investigations also support the clinical finding of a benign course of bradycardia in AMI (2 15) These investigators found that moderately severe bradycardia accompanying experimental AMI in dogs did not predispose to serious arrhythmias On the contrary bradycardia increased the electrical stability of the myocardium at least in a dual way 1) Increasing heart rates during ischemia reduced the ventricular fibrillation threshold 2) The disparity of refractory periods is greater at faster rates during ischemia These effects may indeed explain the potentially dangerous effect of atropine during AMI The same investigators also found that although atropine was highly effective in abolishing benign ventricular arrhythmias in a bradycardia it was considerably less effective in eliminating the arrhythmias associated with the subsequent development of ventricular fibrillation (close coupled premature ventricular contractions) In their model bradycardia also reduced the ischemia in the myocardium and the extent of myocardial necrosis was always found to be increased by cardioacceleration induced by atropine These findings might be of therapeutic importance

A recent clinical report (7) suggests that this may be so as patients with coronary artery disease affecting two and three arteries showed no increase in myocardial blood flow in response to atropine induced cardioacceleration Atropine might thus aggravate myocardial ischemia in patients with occlusive artery disease The possible benefits of cardioacceleration with atropine must therefore be balanced against the potential of the drug for increasing myocardial ischemia The exact mechanism responsible for the production of ventricular irritability after atropine injection is not entirely clear Certainly an increased myocardial oxygen requirement secondary to increased heart rate appears to be an important factor The fibrillation threshold is lowered and the disparity of refractory periods becomes greater at faster rates when the myocardium is ischemic This increase in disparity will lead to slow non homogenous spread of impulses resulting in reentrant activity and eventually ventricular fibrillation Moreover the efflux of potassium from the myocardial cells associated with tachycardia is also known to promote ventricular irritability by bringing the resting potential down towards the threshold potential

Regardless of the basic mechanism involved in the development of ventricular arrhythmias our experience suggests in agreement with reports by others that i v atropine in doses of 0 5 mg and more may be associated with serious arrhythmias in patients with coronary heart disease Because of this potential danger atropine should probably be given only if the bradycardia is severe and associated with hypotension or circulatory instability

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Acute Myeloid Leukaemia Appearing in Two Patients after Prolonged Continuous Chlorambucil Treatment for Wegener's Granulomatosis

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ABSTRACT Two patients with Wegener's granulomatosis have been treated with chlorambucil and prednisolone continuously for 3 and 5 years, respectively This treatment was effective in controlling the disease, but bone marrow toxicity with severe pancytopenia developed in both cases Both patients died from thrombocytopenia with haemorrhagic pericarditis In one case, the diagnosis of acute myeloid leukaemia was established from the appearance of myeloblasts in the peripheral blood and from characteristic bone marrow morphology In the other case this diagnosis was strongly suspected on the basis of the bone marrow morphology alone It is proposed that this development of acute leukaemia in two patients with a primary non neoplastic disease may result from a direct carcinogenic action of chlorambucil in humans

In recent years many reports have been published on the development of malignancies particularly lymphomas and reticulum cell sarcomas in patients treated with alkylating agents or immunosuppressive drugs (6–10 12 15 18–23 25 26 28 30 32–37) In many cases these patients had been treated either because of neoplasms (7 8 12 15 22 28 37) or after transplantation (18 20 26) situations in which an increased risk of development of malignancies may exist (31) We report here the occurrence of acute myeloid leukaemia in 2 out of 8 patients treated with chlorambucil because of Wegener s granulomatosis a non neoplastic disease

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CASE REPORTS

The early courses of these 2 patients have been reported in a previous publication (2)

Case 1 (case 3 in the earlier report (2))

The patient was a male automobile test-driver born in 1919 No case of haematologic malignancy is known in his family In Feb 1967 he developed bilateral otitis media and atrophic rhinitis Repeated biopsies of the septal mucosa showed intense inflammatory reaction with pronounced infiltration of lymphocytes and plasma cells No granulomatous changes and no arteritis were seen

In Jan 1968 a chest X ray revealed several round well demarcated infiltrates 1–2 cm in diameter in both lungs ESR was 70 mm/h Hb concentration 13 2 g/100 ml WBC 9800/μl platelet count 420000/μl and the blood smear was unremarkable Cytologic examination of the bone marrow revealed a normal myelopoiesis with normal maturation A persistent microscopic haematuria was noted The glomerular filtration rate (1) was 92 ml/min/1 73 m² serum creatinine 0 7 mg/100 ml A percutaneous needle biopsy of the kidney in May 1968 showed proliferative and fibrotic changes in most glomeruli Pronounced interstitial cellular infiltration was seen in one area with probable granuloma formation including one giant cell On the basis of the changes in the lung nose and kidney the diagnosis of Wegener's granulomatosis was felt to be strongly supported and therapy with prednisolone 60 mg/day was begun the dose being gradually decreased to 15 mg/day

In April 1969 severe headache and vomiting prompted a neurological investigation The protein content of the cerebrospinal fluid was increased to 82 mg/100 ml and electrophoretic investigation indicated damage to the blood–brain barrier The findings at pneumoencephalography and bilateral cerebral angiography were normal

In July 1970 the patient was admitted to Medical Department V Sahlgren s Hospital for a therapeutic trial with chlorambucil A repeat renal biopsy showed changes similar to those seen 2 years earlier The glomerular proliferation was not very intense and glomerular hyalinization was seen in more than half the glomeruli Arteritis

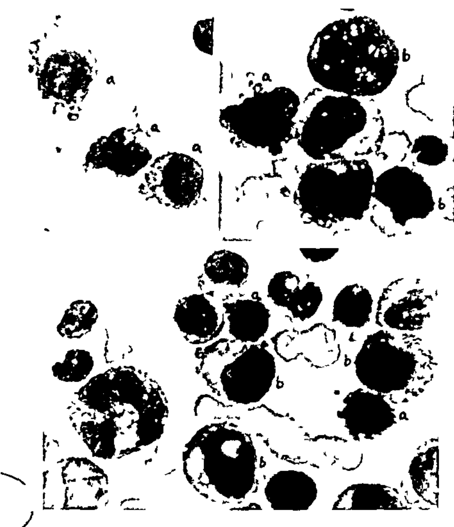


Fig 1 Pathological myelopoiesis from bone marrow smears in case 1 three years after chlorambucil treatment had started a=micromyeloblasts b=myelocytes with marked vacuolization

or arteriolitis were not seen Serum creatinine was 1 3 mg/100 ml and the glomerular filtration rate had decreased to 53 ml/min/1 73 m² Treatment with chlorambucil was started at a dose of 10 mg/day (0 14 mg/kg b wt /day) in addition to the previous therapy of 10 mg prednisolone Hb concentration was 12 0 mg/100 ml WBC 11 000/μl platelet count 365 000/μl ESR 54 mm/h Chlorambucil 8–10 mg/day and prednisolone 7 5–20 mg were given for 2½ years Because of severe symptoms of duodenal ulcer the patient had to undergo a vagotomy in Sept 1971

At the beginning of 1973 the patient rapidly developed a severe pustular psoriasis disseminated all over the body except the face and neck Two months later a herpes zoster was diagnosed in the left sacral area engaging the perineum scotum and penis Cystoscopy revealed herpetic lesions in the left half of the bladder with total lack of detrusor activity at cystometry

Severe pancytopenia was found in Jan 1973 and multiple blood transfusions were required The chlorambucil treatment was discontinued The WBC remained below 3 000/μl with absolute and relative lymphopenia and the platelet count was below 50 000/μl often with values as low as 2 000/μl From March until June the peripheral blood smear showed an increasing number of myeloblasts often around 40 % A few Auer bodies were seen Three examinations of bone marrow smears were performed all showing essentially the same picture (Fig 1) The myelopoiesis was increased showing 9–17 % myeloblasts and 5 % atypical blasts possibly micromyeloblasts The cells of the myeloid series showed strongly increased pleomorphism pronounced dissociation of maturation and abundant nuclear atypies Peroxidase staining showed 73 % of the cells to be positive The bone marrow was interpreted as showing a relatively myeloic leukosis

The condition of the patient deteriorated rapidly No attempt to treat his leukaemia was made because of the thrombocytopenia and his debilitated condition He died in June 1973

The postmortem examination showed that the patient had died from an extensive haemorrhagic pericarditis Microscopic examination of bone marrow from one vertebra iliac bone and sternum revealed a very prominent early myelopoiesis with only a slight degree of differentiation Leukaemic infiltrates were found in spleen liver and kidney The diagnosis of myeloblastic leukaemia was con

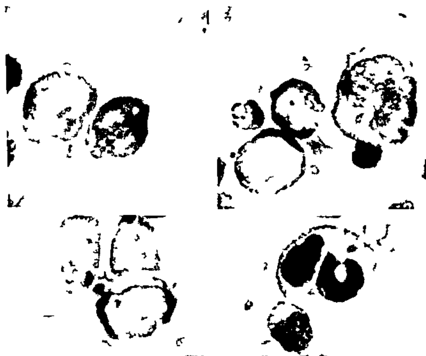


Fig 2 Pathological myelopoesis from bone marrow smears in case 2

firmed There was no evidence of granuloma formation or vascul t s in k dney or lung t ssues

The cumulated dose of chlorambucil rece ved by th s patient was 6 0 g

Case 2 (case 1 in the previous report (2))

The pat ent was a previously healthy male storeman born n 1912 No case of mal gnancy was known in the family In Feb 1966 he developed a low-grade fever and a sore throat S gns of bilateral otitis med a were found In April 1966 a round well demarcated parenchymal infiltration 4 cm in d ameter was found in the upper hilar region of the left lung Biopsy obta ned through bronchoscopy and thoracoscopy showed only unspecif c inflammat on The urinary sed ment was normal

On the susp cion of a lung neoplasm wh ch seriously affected the vent lat on 2 g cyclophosphamide was given i v in May 1968 This was followed by a striking im provement n the general well be ng of the pat ent and the pulmonary infiltrates had almost d sappeared by Aug 1966

In Feb 1967 the patient was admitted to the Med cal Department V at Sahlgren s Hosp tal because of deterioration of his renal function A m croscop c haematuria was observed and ? 3 g prote n/day was excreted in the urine Serum creatin ne was 7 0 mg/100 ml A percutaneous re nal b opsy was performed The glomerul showed th cken ng of the basement membrane cellular prol feration and focal fibrino d necros s Local infiltrates of mononuclear cells were observed in the interstitial t ssue The microscop c appearance was compatible w th the d agnos s of Wegener s granulomatos s Chlorambucil 15 mg daily and prednisolone 60 mg daily were started immediately after admission The dosage was rapidly tapered for both drugs The kidney function improved dramatically and the serum creatin ne decreased to 2 1 mg/100 ml The patient was in good health working full time from June 1967 until March 197? He was treated w th prednisolone 7 5 mg/day and chlorambucil 5 mg/day The chloram buc l treatment was d scontinued in Sept 1971 because of bone marrow hypoplasia with peripheral leukopenia and thrombocytopenia In April 197? the patient was readmit ted because of increasing symptoms of rhin tis and be cause of thrombocytopenia

During the final month the patient was febrile but blood and urine cultures were negative ESR and serum creatinine ncreased and it was felt that his original disease had exacerbated An attempt was made to institute azath oprine but the cond tion of the patient d d not m prove The patient d ed with a general circulatory col lapse The postmortem examination revealed haemor rhage in the myocard um and haemorrhagic pericard t s

A bone marrow smear obtained n 1967 before the treatment with chlorambucil showed only moderate non specif c toxic changes Bone marrow smears were ex am ned on two occas ons after the d scontinuat on of chlorambucil treatment The myelopo es s was immature with remarkably strong polymorph sm pronounced d s sociation of maturat on and variations in the granulation and a few cells with Auer bod es (F g ?) Some of the myeloblasts were atyp cal w th irregular nuclei and con fluent nucleol It was concluded that the pronounced d sturbance of maturat on observed in the smears gave strong reason to suspect a relatively mmature myeloid

leukosis Repeated blood smear examinations during the last month showed myelocytes and a few nucleated red cells but no blasts in the peripheral blood

The total amount of chlorambucil taken by the patient was 8 5 g

DISCUSSION

The diagnosis of acute myeloid leukaemia seems to be firmly established in case 1 The appearance of blasts in the peripheral blood in a person with leukopenia together with increased myelopoiesis severe maturation inhibition and dissociation in maturation of the myeloid cells give sufficient ground for the diagnosis In case 2 the changes in the bone marrow were equally severe but no blasts were seen in the peripheral blood We regard the diagnosis of acute myeloid leukaemia in this case as very likely but not firmly established

The unexpected development of the 2 cases reported here has prompted us to review our total experience of Wegener s granulomatosis and mid line granuloma Since 1966 9 cases of Wegener s granulomatosis and 4 cases of midline granuloma have been diagnosed at this hospital and at the Hospital for Infectious Diseases in Gothenburg Seven of the patients with Wegener s granulomatosis and one patient with midline granu loma were treated with chlorambucil One of the former (case 4 in our previous publication) died r 3 years of treatment with chlorambucil with a ire of thrombocytopenia and general bleeding No bone marrow examination was performed One patient with midline granuloma died after 3 years of treatment with chlorambucil also with severe pancytopenia and with bleeding problems In this case postmortem examination showed severe bone marrow aplasia and signs of toxic changes in the myelopoiesis but no convinc ing evidence of leukaemia

Children with certain types of immunodeficiency disorders (17 24) have an increased tendency to develop malignant tumours particularly malignant lymphomas Patients transplanted with kidney or liver grafts and immunosuppressed with azathioprine and anti lymphocyte serum show a particu larly high incidence of malignant lymphomas (20 26) This experience has been applied to support the hypothesis that immunosuppression even in clini cal circumstances increases the risk of malignancy However transplantation per se may increase the incidence of lymphomas even in the absence of immunosuppression Transplantation is the cause of an intense chronic antigenic stimulus With the grafted organ viable lymphocytes are also trans planted which may cause a chronic low grade graft versus host disease These mechanisms may contribute to the development of lymphomas in transplanted patients (31)

A few cases of neoplasms have been reported in patients treated with other cytotoxic drugs for non malignant diseases such as skin diseases Two patients treated with cyclophosphamide for psoriasis are known to have developed a transi tional cell carcinoma of the bladder (37) Several patients treated for psoriasis with methotrexate have been reported to develop different types of solid tumours (9 19 23) The problem of malig nancies developing in patients treated with im munosuppressive or cytostatic drugs has recently been reviewed by Waldenström (36) He also re ports one patient who after busulphan treatment for psoriasis developed acute myeloid leukaemia Fosdick et al (16) treated 108 patients for rheumatoid arthritis with cyclophosphamide for long periods One of their patients developed chronic lymphatic leukaemia

Wegener s granulomatosis is not regarded as a neoplastic disease Many patients with this disease have survived for several years (11 14) but no case of leukaemia has been reported It seems reasona ble to ascribe the development of acute myeloid leukaemia in our 2 patients to the drug given i e to chlorambucil This may then be regarded as evi dence for the carcinogenic potential of chlor ambucil Like other alkylating agents chlorambucil is a potent inducer of neoplasms in laboratory ani mals (29)

Five other cases have been published of acute myeloid leukaemia appearing after treatment with chlorambucil Four patients were treated for chronic lymphatic leukaemia (15 22) one for macroglobulinaemia (28) Whether or not the treat ment in these cases should be held responsible for the development of acute leukaemia is conjectural Acute myeloid leukaemia has developed in a con siderable number of patients treated with the closely related drug melphalan mostly for multiple myeloma (8 28 36)

Two children who had been treated for renal dis ease with proteinuria with a combination of chlor ambucil and 6-mercaptopurine are known to have developed acute leukaemia (Broyer personal com

munication) One of these children was diagnosed as suffering from acute myeloblastic leukaemia 10 months after the end of the chlorambucil treatment The other child had in addition received nitrogen mustard and methyl bis chlorethylamine All cytotoxic therapy was stopped 3 years before a severe anaemia led to the discovery of an acute leukaemia with a double population of cells lymphoblastic and myeloblastic

In view of this experience of chlorambucil we have changed the long term treatment of our Wegener patients from chlorambucil to azathioprine in combination with prednisolone The few reports on the development of neoplasms in patients treated with azathioprine and prednisolone outside the transplant situation (13 23 30 32 33) do not indicate an increased risk of malignancy in such patients although this possibility cannot be excluded The long term efficacy of azathioprine–prednisolone treatment in Wegener s granulomatosis remains to be tested (3–5 14 27) Fauci and Wolff (14) and Dornfeld et al (11) have managed to induce complete remissions in their patients using cyclophosphamide Many of their patients have been off cyclophosphamide for several years after discontinuation of therapy without relapse These excellent results make cyclophosphamide the most attractive drug for the initial treatment of Wegener s granulomatosis When treatment must be prolonged for several years azathioprine should be considered

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EDITORIAL

Toxicology in Clinical Medicine

The present number of the Acta contains seven papers all treating toxicological topics This seems to me a very favourable sign of interest in these important problems We have a number of other accepted manuscripts on similar topics that will appear in the next numbers of the journal Without any doubt such communications will become increasingly relevant in the future when the cornucopia of potent—and therefore potentially toxic—drugs will be steadily replenished

One of the difficulties inherent in this situation is the fact that the new drugs pose new problems for the doctor It is quite clear that we need a continuing education of the medical profession in order to get acquainted with all the side effects Clinical pharmacology is one of the important new subjects in the medical curriculum but doctors who were educated before this subject was introduced will have to follow publications in medical journals There are several excellent presentations such as the Medical Letter The Medical Letter Inc 56 Harrison treet New Rochelle N Y 1081 USA One classical tbook that appears in new editions with regular inter ls is Sven Moeschlin s Klinik und Therapie der Vergiftungen Georg Thieme Verlag Stuttgart 1972 In a Skandia Symposium from 1972 Suicide and attempted suicide many toxicological problems are also treated Another excellent source of information that may be used in acute situations is the Poison Information Center at the Karolinska Hospital in Stockholm There is a day and night service on the direct telephone line 90000 During the 10 years this center has been active the number of yearly calls has increased from 6000 to 27000 showing that the institution has become very popular

For many years I have stressed the point that a *syndrome never described before is very probably iatrogenic* Toxic substances may cause quite bizarre symptoms and it is always important to take a very careful history of possible previous drug intake often with a real cross examination in such patients Many recent presentations of this subject have stressed the fact that there is too much reliance on toxicity tests in animals They may be quite misleading in several directions Very often the doses given are much in excess of the dosage in human medicine This may give a large number of false positives and delay the introduction of important and possibly life saving new drugs On the other hand such experiments may also give false negatives as there is a great difference in this respect between mice and men Keen observers at the bed side have often made fundamental new contributions thus saving thousands of lives when their results—often much too slowly—have been accepted by the medical community Striking such examples may be quoted from all fields of medicine The mortality from agranulocytosis practically went down to zero when it was found that aminopyrine (pyramidon) and similar drugs were the cause The nephrotoxic effect of phenacetin was established from observations on patients Another example is the death rate in acute porphyria that has been reduced to very low values since it became known that these patients are sensitive to a number of synthetic drugs It is frightening to realize that we still see deaths from the administration of such drugs because doctors do not care to avoid them in sensitive patients Also the fact that so many potent drugs are resting in drawers where they can be found and consumed in large quantities for suicidal purposes is another important aspect of toxicology and it becomes increasingly important for the physician to realize the possibility that several drugs may be combined in suicidal attempts This makes the pattern difficult to recognize and increases the importance of a competent biochemical analysis

A wave of criticism against modern polypharmacy is at the present moment sweeping over the Western countries This is a sound reaction against the combination of drugs that is often seen especially in elderly patients and there is no question that a large number of persons in modern society live in a state of slight chronic drug poisoning The easy availability of drugs especially economically has favoured this development and the fact that such patients often get prescriptions from many doctors *who do not know about each other* is another factor *It would* be a sound arrangement if the doctor discusses the whole pharmaceutical arsenal in the patient s home before he prescribes new drugs The old dictum primum nil nocere is no longer valid If a drug in normal dosage has therapeutic effects it is very improbable that large doses are not in some way toxic

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Jan G Waldenström

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Resumption of Work after Acute Myocardial Infarction

Erik Kjoller

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ABSTRACT A total of 644 patients admitted to the Coronary Care Unit of a district hospital on account of acute myocardial infarction, have been discharged during a 3-year period Of these patients, 71 % had been employed at the time of the infarction and more than 80 % of this group returned to work Among the long term survivors (LTS) aged less than 65 years who had been employed at the time of infarction 87 % of the male and 74 % of the female patients had resumed work some time afterwards Among 347 LTS age was found to be the main factor to determine whether or not patients would be able to resume work, whereas the number of experienced infarctions as well as signs and/or symptoms of heart failure during the acute phase were of no consequence The occurrence of additional symptoms of ischaemic heart diseases (recurrences of infarction, presence of angina pectoris, demand for drugs) was of prognostic importance for whether or not patients would have to abandon work The ability of patients to resume their previous work depended on the character of the latter, i e its type and the physical strain involved About 80 % of the LTS resumed work within three months Patients in whom heart failure had occurred during the acute phase tended to return to work later than those without this complication No more than half of the LTS who had abandoned work declared that cardiac symptoms had been the reason

Three factors are of special interest in matters concerning the long term prognosis of patients who are discharged from hospital after acute myocardial infarction (AMI) the long term survival the state of health of long term survivors and their rehabilitation

The object of the present study is to check whether certain medical and social variables influence the prospect of patients returning to work to establish the time lag between discharge from hospital and return to work and to explain why some patients do not return to work The long term survival has been described in a previous paper (4)

PATIENTS AND METHODS

The selection of patients and the methods used for examination at follow up have been described in detail elsewhere (4) and only the main features will be outlined here In the period Oct 1966–Oct 1969 a total of 927 cases of AMI were admitted to the Coronary Care Unit Copenhagen County Hospital in Glostrup Mortality during hospitalization amounted to 26 % All patients in whom AMI was suspected on their arrival at the admission ward were referred to this department (in this county all patients in whom AMI is suspected are admitted to hospital) Prior to discharge the patients were told not to return to work for one month No special rehabilitation programme was offered

The short time survivors (STS) 644 patients were discharged from hospital about three weeks after the infarction Follow-up for mortality was 100 %

Among the long term survivors (LTS) 477 patients who were still alive at the time of the follow-up 452 appeared for a follow up at the Out patient Clinic three were visited in their homes and questionnaires were sent to 22 who all returned their replies Follow-up of these patients was usually carried out after intervals covering on an average 25 6 months after an AMI (S D 8 7 min 12 5 max 50 3) The following data were obtained on this occasion 1) Employment immediately before the occurrence of infarction and the present conditions of employment 2) Type of work performed before and after the AMI as well as the physical strain implied in the work 3) Time lag between discharge from hospital and resumption of work 4) In the case of patients who had abandoned work when they had done so and why Patients were considered to be employed if they were working for more than four hours a day and regarding women if they managed the domestic work in households comprising two or more persons

At the time of follow-up a total of 167 patients had died—late deaths (LD) Their data concerning employment prior to death were obtained from death certificates hospital records general practitioners and relatives

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Data concerning the occupational circumstances of patients who had died during the period preceding the follow up appear from Table II These data however are subject to considerable uncertainty for one thing because they were obtained after the patients concerned had died (occasionally even a long time after) for another because of the variable reliability of sources from which such data were obtained The tendency is identical in the LD and LTS groups Owing to this uncertainty involved in data applying to patients in the LD group the following paragraphs will be concerned exclusively with facts applying to LTS

Influence of age and cardiac symptoms on return to work

As expected the number of patients who abandoned work during the period preceding the follow up rises parallel with advancing age (χ^2=26 4) (Table III) This is equally true of patients who abandon work immediately after an AMI and of those who return to work but give it up later

The number of infarctions experienced at the time of discharge from hospital does not determine whether or not patients return to work immediately after an AMI and the same applies to signs and/or symptoms of heart failure occurring during the acute phase and the demand for drugs (digitalis and/or diuretics) (χ^2<3 0) It cannot be predicted on the basis of the variables enumerated here whether patients prefer to abandon work after a primary attempt to resume it On the other hand it was noted at follow up that a recurrence of infarctions after discharge the presence of angina pectoris and a demand for drugs might be factors of prognostic significance in deciding whether patients who returned to work after leaving hospital had to give it up again later (χ^2>5 8)

Table III *Influence of age on capacity to resume work after acute myocardial infarction (long term survivors)*

Pats (%)	Age group (y) <50	50–59	60–64	≥65	Total
Abandoned work					
Immediately after AMI	6	18	21	24	16 1
Later	5	8	21	20	11 5
Total					
Abandoned work	11 6	25 7	42 8	43 5	27 6
Employed at the time of follow up	88 4	74 3	57 2	56 5	72 4
Total					
%	100	100	100	100	100
No of pats	95	136	70	46	347

The incidence of recurrences during the follow up period was found to be higher among patients who had abandoned work immediately after an AMI than among those who had returned to work immediately after the episode it was also observed at follow up that the incidence of angina pectoris was highest in the former group (χ^2>6 9) The demand for drugs at the time of follow up was identical in the two groups

Character of previous work as a factor to determine whether or not patients return to work

The various types of work in which patients are employed and the physical demands implied are shown in Tables IV and V

Table IV *Interrelation of type of previous work and return to work (long term survivors after acute myocardial infarction)*

Type of previous employment (%)	Employed at time of follow up	Not employed at time of follow up	Total %	No of pats
Head of department	87	13	100	67
Functionary	66	34	100	95
Casual labourer	59	41	100	63
Small business	72	28	100	53
Miscellaneous	74	26	100	27
Housewife	83	17	100	42
Total	72 4	27 6	100	347

Table V *Previous physical work as a determinant of whether or not patients return to work (long term survivors after acute myocardial infarction)*

Previous work	Present work: No physical	Physical: Light	Physical: Medium	Physical: Hard	Total employed at time of fol low up	Abandoned work: Immedi ately af ter AMI	Abandoned work: Later	Total: %	Total: No of pats
No physical	73	6	4	2	85	5	9	100	124
Physical									
Light	8	63	8	0	79	11	10	100	63
Medium	*6*	*21*	*42*	*2*	*71*	*19*	*10*	*100*	*86*
Hard	4	10	14	20	48	34	18	100	73
Total	29 8	21 1	16 2	5 4	72 5	15 9	11 6	100	346

The type of work previously performed by the patients decides whether those who survive an AMI will be able to return to it (Table IV) Patients who most generally return to work after an AMI are those who hold responsible positions or have a business of their own In this context it should be mentioned that prospects are least favourable for casual labourers In the case of patients who abandon work immediately after an AMI the tendency is the same though not at a level of significance

The different rates at which patients in the various groups returned to work cannot be ascribed to a different distribution according to age in the individual groups or to a presence of different factors that otherwise are of long term prognostic value (e g number of previous infarctions signs and/or symptoms of heart failure during the acute phase and demand for drugs at the time of discharge) The different rates at which work is resumed by patients belonging to different social strata cannot be ascribed to a difference in the rate of recurrences during the follow up period or to a different incidence of angina pectoris or demand for drugs at the time of follow up

Studying rehabilitation in relation to the degree of physical strain involved in the previous occupation (Table V) it will be noted that no more than 48% of those hitherto employed in physically hard work had returned to work by the time of the follow up as opposed to 85% of those employed in work not requiring physical efforts The main reason is that many patients who had been employed in physically hard work had left it immediately after onset of an AMI Differences in the rate at which work was resumed by patients in the two groups i e patients whose work involved no or only a moderate physical effort and those whose work actually was hard or moderately hard cannot be ascribed to a difference in the age and sex distribution of patients or to differences in parameters otherwise of value for the long term prognosis ($\chi^2<0$ 8)

The fact that a relatively large number of patients employed in hard or moderately hard work left it after an attempt to resume it cannot be explained by a potential presence of a greater number of factors otherwise of prognostic value or by a higher incidence of recurrences during the period of follow up At follow up the incidence of angina pectoris and the demand for drugs were found to be identical in the two groups of patients i e those employed in hard or moderately hard work and those not employed in hard work By the time of the follow up a majority of patients were employed in work just as hard as that previously performed

Time lag between discharge from hospital and return to work

As a rule patients were told to take a month off before they might return to work The interval before patients resumed work if at all appears from Table VI It will be noted that less than 80% returned to work within three months at the same time 93% of all those who returned to work did so within the course of six months The age of LTS had apparently no influence on the length of the interval between discharge from hospital and return to work

The group of patients who returned to work later than three months after discharge from hospital does not deviate from the other groups as regards number of previous infarctions or demands for

drugs at the time of discharge On the other hand the presence of signs and/or symptoms of heart failure during the acute phase seemed to indicate that the patients concerned would not resume work until late stages ($\chi^2=4.1$)

Reasons why patients abandoned work

By the time of the follow up 96 of the LTS who had been in employment at the time of the infarction had abandoned work The reasons are given in Table VII Only 37% of the patients declared that cardiac symptoms had been the causative factor It was claimed equally often that angina pectoris and/or dyspnoea on exertion were the reasons Patients who had abandoned work immediately after the infarction and those who had returned after the episode but later left it again claimed equally often that cardiac symptoms had been their main reason for abandoning work In 19% of the cases the main reason was that a general practitioner in the course of a routine check had advised the patients to abandon work

Of the 347 LTS who had been in employment when the infarction occurred only 6 3% had abandoned work immediately after the AMI because of cardiac symptoms and of the 291 patients who resumed work after the myocardial infarction only 4 8% had to abandon work later on account of cardiac symptoms Of males aged less than 65 years at the time of the infarction 5 8% had abandoned work immediately after the episode and 5 3% later for the same reason

The group of patients who abandoned work on account of cardiac symptoms (or upon the advice of a general practitioner) and the group comprising all other patients who abandoned work do not deviate as regards distribution by sex and age number of previous infarctions signs and/or symptoms of heart failure during the acute phase or demand for drugs at the time they left hospital The incidence of symptoms indicating ischaemic heart diseases (IHD) including recurrences of infarction and/or presence of angina pectoris was equally high in the two groups at the time of follow up ($\chi^2<1.5$)

Table VI *Interrelation of age of patients and time at which work is resumed (long term survivors after acute myocardial infarction)*

Time lag between discharge from hospital and return to work (mo)	Age group (y)			Total
	<50	50–64	≥65	
≤1	44	35	51	39 9
1–3	41	44	17	39 5
4–6	10	14	20	13 4
7–12	3	5	6	4 8
>12	2	2	6	2 4
Total				
%	100	100	100	100
No of pats	89	167	35	291

Table VII *Main reasons why work was abandoned immediately or later after an acute myocardial infarction (long term survivors)*

	Abandonment of work (%)		
	Immediately after an AMI	At later stages after AMI	Total
Cardiac indications			
Angina pectoris and/or dyspnoea on exertion	39	35	37
Doctor s advice	25	10	19
Absence of cardiac indications			
Voluntarily or on account of diseases other than heart diseases	30	35	32
Old age pensioners	6	20	12
Total			
%	100	100	100
No of pats	56	40	96

DISCUSSION

Several variables have been used with a view to predicting the prospects of occupational rehabilitation of patients with AMI According to Garrity (2) these variables may be classified into three categories medical sociodemographic and sociopsychological In the present study attention has been focussed on a few variables from the first two groups

One of the main objects of the present investigation has been to obtain an impression of the degree of incapacity of patients after an AMI the series is composed of patients from a suburban area where most cases of AMI are presumably recognized and recorded it was collected at a time of full employment and the prevailing system of social security

functioned satisfactorily no specific rehabilitation programme was offered to the patients

In general the rate at which patients returned to work was comparable with that observed by other investigators (1 5 7) The high rate at which work was resumed may in part be explained by the fact that such an urban area offers many possibilities of employment (11)

Methodological problems are always encountered in studies of this type since the occupational circumstances of LD (i e patients who died after they left hospital) cannot be evaluated reliably These cases of LD also imply that the term employment may be related either to the total number of patients who left hospital or to the effective number of patients who by now have prospects of employment Both types of analysis may be applied to the investigation by Sharland (9) who studied a series of male subjects aged less than 60 years in whom infarction occurred and who had been employed prior to this episode As regards the total number of patients the percentage of those who resume work after an AMI is seen to rise to 86% during the first year after the episode after which there is a minor fall attributable to LD (also owing to the fact that one patient primarily returned to work but later abandoned it—abandoned work at a later stage) As compared with the patients who have prospects of resuming work the percentage of those who actually return to work shows a steep r during the first year and a more gradual in later Maximum re employment 96% is not achieved until two years after discharge from hospital

The time lag between discharge and return to work is comparable with that observed by other investigators (3 5 7) So far it remains to be established whether or not age per se has any influence on the rate at which patients resume work Sievers (10) showed that the average length of medically certified inability decreased with age while Shapiro et al (8) found that the rate of work resumption decreased parallel with advancing age When assessed on the basis of the figures reported by Shapiro et al however the differences are rather negligible in fact half of the elderly patients may return to work after relatively long convalescences while the other half apparently resume work at the same rate as young patients In the present study age was not found to be of reliable significance

It was observed in the present study that heart failure might exert some influence on the rate at which work would be resumed A similar phenomenon has been observed by other investigators (3 8) Shapiro et al (8) showed that only a few patients with AMI of severe degree would return to work while many of those with AMI of moderate degree did so Severe degree of infarction is interpreted as follows shock is present overt heart failure is manifest ventricular tachycardia as well as complete atrioventricular block or Adams Stokes attacks are present The results obtained in the present trial are in distinct contrast to the above since LTS in whom heart failure occurred during the acute phase returned to work just as often as patients in whom heart failure had not occurred This difference in degrees of rehabilitation may have arisen because the length of the follow up period differed in the various studies The long observation period in the present study implies that the cardiac status of patients is identical at the time of follow up whether or not heart failure has occurred during the acute phase

This may also explain why rehabilitation of the patients in the present series—as opposed to those in the series of Nagle et al (6)—was equally satisfactory whether an isolated acute infarction had occurred or episodes had preceded the acute infarction

In patients who survive an AMI previous symptoms of IHD and/or complications during the acute phase need not be the sole reason why they abandon work Shapiro et al (8) demonstrated that the percentage of male individuals who were in employment at a given time was only slightly lower among LTS after AMI than among male subjects free from coronary diseases This agrees with the finding that no more than 10% of the LTS in the present series had to abandon work on account of cardiac symptoms

Patients originating in the upper socio-economic strata and/or patients whose work does not imply physical effort or at least only moderate effort were those who most frequently resumed work after leaving hospital A similar phenomenon has been observed by other investigators (5 8 9 11)

As regards the present patients only those failed to return to work in whom additional symptoms of IHD occurred during the follow up period A similar phenomenon has been observed by other investigators (5) Nagle et al (6) found that the inci

ence of angina pectoris three to five months after AMI was equally high in all patients no matter whether they had returned to or had abandoned work

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Characteristics of Representative Male Survivors of Myocardial Infarction Compared with Representative Population Samples

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ABSTRACT A series of 299 men aged 27–67, who had survived their first myocardial infarction (MI) have been compared with representative population samples with respect to tobacco consumption, alcoholic intemperance, physical activity during work and leisure time, occurrence of hypertension and cholesterol and triglyceride levels in serum The infarction patients comprised 90% of all surviving, diagnosed cases of primary MI in men aged 67 years or below during 1968–70 in Göteborg, Sweden The comparison between infarction patients and general population samples revealed that the patients smoked more, and were less physically active during leisure time but not during work They had more often a positive history of hypertension and treatment for high BP and their serum cholesterol and serum triglyceride values were higher For all these variables the difference decreased with increasing age and was generally not statistically significant above the age of 60 years Alcoholic intemperance was more common among infarction patients who died outside hospital but there was no difference in this respect between surviving patients and the general population

When investigating characteristics which predispose for a certain disease prospective studies are often most suitable This method presupposes however that the disease has a relatively high incidence as otherwise a sufficient number of patients cannot be collected within a reasonable time A group of individuals who have already suffered the disease may be chosen instead but the disease may alter certain factors for example the BP after myocardial infarction (MI) and the material may be selective for example due to deaths Selection may also occur in certain cases due to the disease never being diagnosed this being most frequent with trivial disorders that give few symptoms The advantage of studying patients who already suffer from the disease is that a sufficiently large series can be collected relatively rapidly even if the variables in question are infrequent In addition it is easier to investigate a large number of variables

The object of the present study was to compare tobacco consumption alcoholic intemperance physical activity at work and during leisure the occurrence of hypertension and cholesterol and triglyceride levels in serum in men who had survived their first myocardial infarction with representative population samples

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STUDY POPULATION

Patients with myocardial infarction

From Jan 1st 1968 onwards all cases of acute myocardial infarction occurring in the population of Goteborg in certain age groups have been registered by a special organization (17 18 21) The series studied during 1968–70 comprised 90% of all diagnosed surviving infarction patients in the population of Göteborg in the age groups concerned (18) All surviving patients were systematically cared for after the acute phase of the infarction at a special clinic—the Postmyocardial Infarction Clinic (19 79) In the years 1968–69 persons aged 55 years and below were included and in 1970 persons aged 67 years and below

Table I *Age distribution of men at the Post myocardial Infarction Clinic in 1968–70*

Age group	Mean age (y)	Primary infarction (*n*)
–39	35	8
40–44	43	22
45–49	47	63
50–54	52	97
55–59*	57	48
60–64*	62	45
65–67*	66	16
Total		299

* Comprises only patients with MI in 1970

except for a randomly selected 30% sample aged 57–67 years omitted in order to form a control group A total of 299 men with *primary* infarctions were included in the present study The distribution by 5 year age groups and the mean ages of the groups are shown in Table I

Population series

Randomly selected men from different age strata in the population of Goteborg were examined The population samples were obtained from the municipal census list which by law must be kept up-to-date The samples were investigated for various reasons one was used for a prospective population study some were included in a primary preventive trial and some were primarily investigated for use as controls for the infarction patients Table II gives data on the population samples and their index numbers for the following tables The following population samples were used for comparisons with infarction

year-old men

This group consisted of men born in 1924 (sample 1) who were included in the intervention group in a primary preventive trial for cardiovascular disease which started in Göteborg in 1970 (85) and comprised all men born in 1915–22 and 1924–25 and registered in Goteborg The intervention group comprised a random third—almost 10 000 men At the initial examination they were investigated by means of a postal questionnaire and personal interviews and registration of BP cholesterol values smoking habits etc In the total intervention group 83% completed the postal questionnaire and 75% attended the screening examination A detailed analysis of non-participants has been published (82) They were characterized by a somewhat higher prevalence of chronic diseases and alcoholic problems They were more often unmarried

50 year-old men

This series consisted of men from the Study of Men Born in 1913 (sample 2) which is a cross sectional and longitudinal population study and comprises all men registered in *Goteborg and born in 1913 on dates which are multiples of* three i e 3 6 9 12 etc The original sample was subjected to interview and investigation in 1963 Methods and an analysis of drop-outs have been presented in detail previously (68 69) Briefly these non participants also had alcoholic problems more often and were more often unmarried They had on the whole a negative attitude towards medical care These men were examined in 1963 and 1967 In the comparisons below only data from one of these two examinations appear in the same table

In certain cases 50 year old men born in 1921 from the *intervention group of the primary preventive trial* were used as controls (sample 3)

52 year old men

This series originated from the intervention group of the primary preventive trial and comprised men born in 1918 (sample 4)

54 year old men

The series consisted either of men from the Study of Men Born in 1913 investigated in 1967 (sample 5) or of 54 year-old men born in 1916 from the intervention group of the primary preventive trial (sample 6)

58 year old men

The series consisted of men born in 1914 from the Study Karl (sample 7) This was a cross sectional population study of men in Goteborg born in 1906 1910 and 1914 on the 15th and 30th day of each month and was performed in

Table II *Random population samples of men from Goteborg used for comparison with infarction patients*

Sample no	Age of subjects (y)	Size of sample	Non partici pants	Investigated *n*	Investigated %	Year and name of investigation
1	48	965	233	732	76	1972 The Primary Preventive Trial
2	50	973	118	855	88	1963 The Study of Men Born in 1913
3	50	1 123	132	901	80	1971 The Primary Preventive Trial
4	52	938	230	708	76	1971 The Primary Preventive Trial
5	54	855	52	803	94	1967 The Study of Men Born in 1913
6	54	938	244	694	74	1971 The Primary Preventive Trial
7	58	101	13	88	87	1972 The Study Karl
8	62	115	19	96	83	1972 The Study Karl
9	66	114	24	90	79	1972 The Study Karl

1972 An analysis of sick leave data from the Goteborg Social Insurance Office showed no essential differences between participants and non participants as regards number of periods of sick leave or number of days sick during the past five years The number of short periods of sick leave (up to seven days) was greater in the participant group however while the number of long periods (30 days or more) was greater in the drop-out group Sick leave due to cardiac disease was equally common (approx imately 10%) in the participant and non participant groups but sick leave due to high BP was less common in the participant group (3%) than in the non participant group (10%) An analysis of the register of the Temperance Board showed that the non participant group had more often been registered for intemperance (55%) than the participant group (20%)

62 year old men

The series consisted of men born in 1910 from the Study Karl (sample 8)

66-year old men

The series consisted of men born in 1906 from the Study Karl (sample 9)

The Study of Men Born in 1913 was most extensive and had the highest participation rate Therefore this sample was used most often for comparisons When data were available for other samples too these men were included The men from the Study Men Born in 1913 were examined both in 1963 and in 1967 but data from the two occasions were never pooled The measured frequency of some var iables i e known hypertension increased with time pre sumably due to more widespread contact with physicians When this was the case only controls examined as close as possible in time to patients were used for comparisons

METHODS AND DEFINITIONS

Information concerning smoking habits physical activity hypertension known to the interviewee and antihyper tensive medication was obtained by interview and re corded by means of a special questionnaire (17 19 85)

Both the infarction patients and the population samples were interviewed by any of the six physicians working at the Section of Preventive Cardiology at the time of these investigations Highly structured questionnaires were used and the interviewers were trained together in order to avoid internal variation The infarction patients were in terviewed during their hospital stay for the infarct

In the primary preventive trial the case history was obtained mainly by self administered questionnaires sent to the participants by post and returned completed in connection with examination at the hospital the state ments on the questionnaire being checked by a physician in the presence of the subject

Smoking

Persons who smoked ≥1 g tobacco daily or who had smoked to this extent for at least one month up to a time less than three months prior to the interview were clas sified as smokers Ex smokers were persons who had previously smoked ≥1 g tobacco daily for at least one month but had stopped smoking more than three months prior to the interview Individuals who had never smoked regularly to this extent were classified as non smokers One cigarette was considered to correspond to 1 g of tobacco 1 cigarillo to 2 g and one cigar to 5 g For pipe smokers the weekly consumption in g was divided by 7 in order to give the daily consumption in g

Registration by the Temperance Board

In every Swedish commune there is a Temperance Board responsible for registration and rehabilitation of alcoholics (33) Information was obtained from the Temperance Board in Goteborg as to whether the person concerned was registered for intemperance and/or treatment of alcoholism

Physical activity during the previous year

Physical activity at work and during leisure time was estimated separately on 4-point scales at work from 1 (office work sits for more than half the day) to 4 (very heavy work building forestry or agricultural work) dur ing leisure from 1 (passive watches TV reads) to 4 (highly trained active competitive sportsman) (29 79 83) This questionnaire was based upon known levels of energy expenditure for various activities and has been used extensively in various studies

Hypertension

A statement by an interviewee that he had at some time been told by a physician that his BP was too high was registered as a positive history of hypertension

Antihypertensive theraphy

The subject was questioned with regard to antihyper tensive treatment

Blood lipids

Cholesterol in serum was determined according to Cramér and Isaksson (13) and triglycerides according to Carlson (7) In the infarction patients and men from the studies Men Born in 1913 and Karl the blood sample was taken in the morning after 12 hours fasting and both cholesterol and triglycerides were analysed In the primary preventive trial only serum cholesterol was analysed and the blood sample was taken in the afternoon after 4 hours fasting

Statistical methods

The statistical tests of fourfold tables were performed by Fisher s exact test using an approximation of the test variable with Edgeworth s expansion to get the p value (51) Pooling of independent fourfold tables was done with the Mantel Haenszel procedure (46) The p values are calculated with an Edgeworth expansion of the added test variables if these have the same sign The p values multi plied by two are given in the tables

For continuous variables the mean and S D were calcu lated by the usual methods The statistical significance of differences between mean values was determined using Student s t test Differences were considered statistically significant for $p<0.05$

Table III *Smoking habits in men before myocardial infarction and in random population samples*

	Never smoked						Present smokers				
	MI pats		Population				MI pats		Population		
Age group	No /tot	%	No /tot	%	Sample no	Diff (2p)	No /tot	%	No /tot	%	Diff (2p)
–39	0/8	0					6/8	75 0			
40–44	2/22	9 1					18/22	81 8			
45–49	4/63	6 3	231/732	31 5	1	0 001	54/63	85 7	355/732	48 5	0 001
50–54	4/97	4 1	616/2 257	27 3	2+4+6	0 001	86/97	88 7	1 212/2 257	53 7	0 001
55–59	4/48	8 3	19/86	22 1	7	0 066	35/48	72 9	43/86	50 0	0 015
60–64	7/45	15 5	25/92	27 2	8	0 192	27/45	60 0	37/92	40 2	0 045
65–67	6/15	40 0	25/88	28 4	9	>0 20	6/15	40 0	32/88	36 4	>0 20
Pooled											0 001

RESULTS

Tobacco smoking As seen in Table III the number of men who had never smoked was significantly less among the young infarct patients than among the general population In the higher age groups the difference was smaller and not significant In the oldest age group there were more (not significant) men who had never smoked than in the population sample

The percentage of present smokers was higher in all age groups of patients than in the general population but not significant in the oldest age group

Tobacco consumption among smoking men was ... cantly higher among the two youngest age ... of patients than in the general population

Thus for all indices of tobacco consumption there was a tendency to smaller differences between patients and the general population with increasing age

Registration by the Temperance Board could only be compared between patients and the general population for the age group 50–54 in which it was not different for surviving patients For this variable data were however available for infarction patients who died outside hospital and for this group the difference was significant against the general population (Table IV)

The younger infarct cases especially those dying outside hospital had an even higher registration rate than the older Since the registrations by the Temperance Board are cumulated for each person and there are no indications of a higher rate of registrations among young persons in the general population these results point to an even greater difference between infarct patients and the general population in younger ages

Low physical activity at work was not significantly more common among the infarction patients than in the population samples (Table V) The slight tendency towards lower activity among patients up

Table IV *Registration by the Temperance Board of men before a non fatal or fatal (dead outside hospital) myocardial infarction and in a random population sample*

	Hospitalized MI patients			MI patients dead outside hospital			Population		
Age group	No /tot	%	Diff against popul (2p)	No /tot	%	Diff against popul (2p)	No /tot	%	Sample no
–39	3/8	37 5		2/2	100 0				
40–44	4/21	19 0		7/8	87 5				
45–49	10/63	15 9		7/24	29 2				
50–54	17/97	17 5	>0 20	18/52	34 6	0 034	176/852	20 7	2
55–57	6/31	19 4		7/20	35 0				

mokers of ≥15 g/day				
ll pats		Population		
o /tot	%	No /tot	%	Diff (2 p)
4/6	66 7			
5/18	83 3			
8/54	70 4	146/355	41 1	0 001
2/86	60 5	447/1 212	36 9	0 001
6/35	45 7	21/43	48 8	>0 20
0/27	37 0	11/37	29 7	>0 20
2/6	33 3	12/32	37 5	>0 20

to the age of 64 years was not even significantly different from the population samples after pooling of the p values (see Methods)

Low physical activity during *leisure time* was significantly more common among the infarction patients than in the population samples in the age group 50–54 (with large numbers of patients and controls) The differences between patients and controls in other ages were generally fairly small and not consistent

Previous information from a physician about *hypertension* not necessarily treated was more common in all age groups of patients than in the population samples but the difference was significant only for the age group 50–54 and the pooled groups The frequency of known hypertension increased on the whole with increasing age for both patients and controls (Table VI)

Antihypertensive treatment showed the same tendency as known hypertension (Table VI) Both among patients and in the general population in younger ages roughly 50% of those with known hypertension were on treatment whereas in older ages the percentage was considerably higher

The mean values for *serum cholesterol* (Table VII) decreased with increasing age in the series of infarction patients but the mean values did not change with age in the population samples from the age of 45–49 to 65–67 Thus the difference between patients and population samples decreased with increasing age The difference was significant up to the age of 55–59 years

The serum *triglyceride* values (Table VII) were rather constant for increasing ages among the infarction patients In the population samples however values increased with increasing age Thus there were significant differences only in the age groups 50–54 and 55–59 (60–64 nearly significant) Significant differences would probably have been found in the youngest age groups too if controls had been available

DISCUSSION

In the present investigation men who survived their first myocardial infarction were studied in detail and compared with men from the general population with the object of identifying characteristics for the patients Men were selected partly due to the higher incidence of MI in them compared with women for ages up to 70 and partly because women

Table V *Low physical activity during work and leisure in men before a myocardial infarction and in random population samples*

Age group	Low physical activity during work						Low physical activity during leisure					
	MI patients		Population				MI patients		Population			
	No / tot	%	No / tot	%	Sample no	2 p	No / tot	%	No / tot	%	Sample no	2 p
–39	4/7	57 1					6/7	85 7				
40–44	10/16	62 5					12/16	75 0				
45–49	40&53	75 5	498/732	68 0	1	>0 20	48/53	90 6	599/732	81 8	1	0 140
50–54	58/82	70 7	1 618/ 2 372	68 2	3+4+5	>0 20	80/84	95 2	2 031/ 2 372	85 6	3+4+5	0 011
55–59	38/48	79 2	58/85	68 2	7	>0 20	46/48	95 8	77/86	89 5	7	>0 20
60–64	30/43	69 8	51/84	60 7	8	>0 20	35/45	77 8	81/88	92 0	8	>0 20
65–67	9/16	56 3	45/70	64 3	9	>0 20	16/16	100 0	82/85	96 5	9	>0 20

Table VI *Known hypertension and antihypertensive treatment in men before a myocardial infarction and in random population samples*

	Known hypertension						Antihypertensive treatment					
	MI pats		Population				MI pats		Population			
Age group	No / tot	%	No / tot	%	Sample no	Diff (2 *p*)	No / tot	%	No / tot	%	Sample no	Diff (2 *p*)
–39	0/8	0					0/8	0				
40–44	1/22	4 5					0/22	0				
45–49	11/63	17 5	86/732	11 7	1	>0 20	5/62	8 1	37/732	5 1	1	>0 20
50–54	26/97	29 9	311/ 2 303	13 5	3+4+6	0 001	15/97	15 5	154/ 2 303	6 7	3+4+6	0 005
55–59	10/48	20 8	8/88	9 1	7	0 099	7/48	14 6	6/85	7 1	7	>0 20
60–64	11/45	24 4	17/96	17 7	8	>0 20	9/45	20 0	13/91	14 3	8	>0 20
65–67	5/16	31 3	15/90	16 7	9	>0 20	5/16	31 3	9/87	10 3	9	0 079
Pooled						0 001						0 001

in Göteborg who survived infarction have already been subjected to a special study (2)

The infarction series studied was limited to men aged up to 67 due to the observation that many of the risk factors are more strongly associated with MI at lower ages With increasing age the importance of the traditional risk factors thus declines This is the first study in which a representative material of men who survived an MI in a large well defined population has been thoroughly studied from the time of onset and prospectively

Studies of individuals who die of MI before coming under medical attention are much needed …sons who die in the early phase of infarction … to differ from those who survive A prospec… …e study has shown that the risk factors for fatal and non fatal MI are partly different (72) Such differences are further illustrated by the finding that a multiple risk function for death not more than two years after the onset of infarction could not predict non fatal reinfarction within the same period (74)

In the present study it was found that those who died in the early phase were more frequently registered by the Temperance Board from which it may be concluded that social alcohol problems were present and probably also excessive consumption of alcohol in the majority of cases Whether the increased risk of death outside hospital was due to alcohol as such or to related factors such as social maladjustment or special personality cannot be determined at present There are however studies suggesting that alcoholics have a predisposition for malignant arrhythmias (56 62) which may be further accentuated by myocardial ischemia It is

Table VII *Serum cholesterol and serum triglycerides in men 3 months after a myocardial infarction and in random population samples*

	Serum cholesterol (mg/100 ml)								Serum triglycerides (mg/100 ml)							
	MI pats			Population					MI pats			Population				
Age group	*n*	Mean	S D	*n*	Mean	S D	Sample no	Diff (2 *p*)	*n*	Mean	S D	*n*	Mean	S D	Sample no	Diff (2 *p*)
–39	8	291	72						8	170	82					
40–44	22	267	44						22	149	51					
45–49	60	287	54	1 583	251	44	1+2	0 001	60	157	81					
50–54	87	272	52	2 272	243	42	3+4+6	0 001	87	161	86	853	108	65	2	0 001
55–59	40	264	46	87	240	45	7	0 007	40	155	76	87	116	58	7	0 002
60–64	34	267	73	91	249	44	8	0 10	34	187	133	91	140	112	8	0 057
65–67	11	248	29	87	253	41	9	>0 20	11	151	47	87	144	113	9	>0 070
Pooled								0 001								0 001

possible that deaths shortly after the onset of infarction may have different backgrounds to those occurring later Coronary thrombosis and/or occlusion are sometimes not present in cases of sudden heart death The explanation may then be a pathological microcirculation or impairment of the function of the conduction system or myocardium (57)

An association between smoking and MI was indicated as early as in 1935 when White (78) showed that all 21 of his male infarction patients aged up to 40 were smokers Since then several studies of male infarction patients aged up to 50 have shown that 90–100% were smokers at the time of the infarction In the studies which include control groups the proportion of smokers among the controls has been 55–80% (15 16 27 34) During the past 15 years prospective epidemiological studies have shown an association between cigarette smoking and increased morbidity and mortality from ischaemic heart disease (IHD) (14 20 32 38 41 59 65 73 86) The increased risk has been most pronounced at younger ages and declined with increasing age though persisting up to the age of 80 (3 14 32 53) Most of the studies have concerned men but an increased risk has also been demonstrated for women (9 31 38 59) In most of the studies the increased risk has been proportional to the number of cigarettes smoked Pipe or cigar smoking has generally not increased the risk (3 32 38) but a slight to moderately increased risk has been shown in some studies (9 59 67 71) In several investigations persons who stopped smoking have revealed a reduced risk within a few years of stopping and have often reached the same risk level as those who had never smoked (31 38 59 71) The association between cigarette smoking and IHD has consistently been shown for fatal MI non fatal infarction and sudden death but not for angina pectoris in studies in which this classification was made (61) An exception however is the study by Shapiro et al (59) showing an association between smoking and angina pectoris The association between smoking and IHD has been shown to be independent of other risk factors such as high BP high serum cholesterol physical inactivity and obesity (39 86)

It has been postulated that the relationship between smoking and IHD might be secondary and mediated for example by personality characteristics which might be inherited or acquired A special type of personality characterized by competitive behaviour, bustle etc —type A—smoked to a greater extent and had a higher risk of IHD than the opposite type of personality—type B (55) It was found however that smokers within type A and type B had a higher incidence of IHD than non smokers from which it must be concluded that type A personality and smoking increase the risk of IHD independently of one another (35)

A few studies have given results which do not accord with those referred to above In a study of monozygotic twins of varying ages discordant with regard to smoking the prevalence of IHD was not higher in the smokers (45) The number of deaths due to IHD among the monozygotic smoking discordant twin pairs was however small (9 and 11 respectively)

In the present study in view of these findings concerning smoking and an increased risk of IHD it was not surprising to find a larger proportion of smokers among the younger infarction patients than in the population sample This may be due to smoking being a stronger risk factor for MI in younger age groups or to the mortality being higher in smokers or to both Another possible explanation might be that the smoking habits in the community alter with time smoking is more common among younger persons today than formerly According to a Finnish study (54) heavy smokers (>25 g tobacco daily) have a higher tendency to sudden death in connection with an acute manifestation of IHD This suggests that the findings in the present study concerning non fatal cases do not overestimate the association between smoking and MI

In the present series of surviving infarction patients the level of physical activity at work and during leisure time tended to be somewhat lower than in the population during the year prior to the interview There are three possible sources of error Selection of surviving patients alone will probably lead to a less pronounced concentration of physically inactive patients since several studies have indicated that the mortality in IHD is higher in physically inactive individuals than in physically active (23 36 49 61) The second source of error exerts the opposite influence i e tends to exaggerate the impression of physical inactivity as a characteristic of individuals during the year preceding MI Some of the patients had symptoms of cardiovascular disease such as angina pectoris dyspnoea and intermittent claudication during the

year prior to infarction and may therefore be suspected of having been physically inactive When patients in the infarction material who had not reported angina pectoris, dyspnoea or intermittent claudication were studied however the proportion of inactive individuals was found to be larger both with respect to leisure and work This means that the level of activity was higher for patients with symptoms than the average for the patients and bias due to this source of error can thus be excluded It is also possible that those who already have suffered an MI tend to underestimate their activity before the infarction A check of the activity history in subjects from the population samples interviewed both before and after an MI does not however support this assumption as an important bias As regards the validity of the method of estimating physical activity ratings according to the questionnaire used in the Goteborg studies showed good correlation to physical performance measured as the proportion of individuals in each activity group who were able to perform a maximal exercise test In the group with a low level of activity at work and during leisure time 63% were able to perform a maximal exercise test compared with 95% of the individuals in the high activity group Exercise tolerance at a pulse rate of 150/min and calculated oxygen uptake also showed good correlation between the activity groups especially with respect to activity during leisure time (83)

The London busmen study has shown that physi inactivity is a risk factor for IHD but the associ seems to be stronger for systolic BP serum cholesterol and smoking (48 49 58) Many other epidemiological studies have also shown physical inactivity to be a risk factor (5, 8 40) Some studies have indicated that it is not until physical activity falls below a certain minimum level—the threshold—that physical inactivity becomes a risk factor (8 47) Physical activity at work and during leisure time in the Study of Men Born in 1913 was assessed in 1967 according to the 4 point scale which has subsequently been applied to population and infarction patient studies in Goteborg After six years follow-up there was an insignificant tendency to a greater number of new infarctions than expected in the group with low activity during leisure time but no relationship with activity at work Persons with a high level of activity during leisure time smoked less and were less frequently registered by the Temperance Board than others (84)

Apart from smoking and high serum cholesterol hypertension is the main risk factor for IHD as has clearly been shown in several studies In most investigations MI was not analysed separately (39 73) but even when this is done hypertension is a distinct risk factor (61 64 76 86) The prevalence of hypertension in infarction series has varied between 20 and 75% (50 60 63) The variation is mainly due to differences in definition and patient series

The BP immediately after an MI is not representative of the individual s BP prior to infarction and it does not return to the preinfarction level until after several months if at all (81) We have therefore in the present study paid attention also to a positive history of hypertension and antihypertensive therapy prior to infarction Since the patients have often had symptoms of chest pain breathlessness upon exertion etc there may be some overrepresentation with regard to knowledge of hypertension and antihypertensive therapy compared to the population due to the patient consulting a physician for these symptoms prior to the infarction and being diagnosed as hypertensive This mechanism cannot explain more than part of the overrepresentation found in the patient material against the population sample regarding positive history of hypertension and antihypertensive therapy Upon calculation of the actual prevalence of hypertension prior to the onset in the infarction patients it was found that approximately half of the hypertensives were aware of their high BP (87) The proportion has been found to be of the same order in the general population (80)

As a reference group for comparison with the patients 50 and 54 year old men from the primary preventive trial were chosen instead of men born in 1913 with respect to hypertension and antihypertensive therapy It was obvious that positive histories of hypertension and of antihypertensive therapy had become much more common between the years 1963 and 1971 It was therefore deemed more correct to compare patients who had suffered an infarction during 1968–70 with a population sample investigated in 1971 than with one from 1963 The proportion of 50-year-old men in the population with a positive history of hypertension in 1963 was 2% compared with 11% in 1971 A positive history of antihypertensive therapy was found in 1 6% of 50-year old men in the population in 1963 and in 5% in 1971 There are no doubt several explanations of

this increase during a period of less than 10 years The most important factors are probably a transition towards lower BP values for diagnosis and therapy among the majority of physicians and increasing use of health examinations

The cholesterol and triglyceride values in serum were determined three months after the acute infarction Serum cholesterol falls rapidly in connection with the acute attack and returns to preinfarction values within a few weeks (11 70 75 77) It has been found in the primary preventive trial in Goteborg that the cholesterol value three months after an MI is largely the same as at screening prior to the infarction (81) Triglycerides rise during the acute phase and then gradually return during the course of several weeks to the preinfarction level (70) Serum lipids are considered to return to the characteristic values for the patient within three months at which time the values presented in this study were obtained (26)

High serum cholesterol is one of the best documented risk factors for IHD (6 10 28 37 42 73 86) Higher serum cholesterol values have consistently been found in male infarction patients than in controls (4 12 22 30 52 66) In female patients who survived MI cholesterol values were however not significantly higher than in a population sample (2) In a recent prospective study it was shown that serum cholesterol was higher in those who subsequently suffered a fatal MI than in those who suffered a non fatal (20)

Many studies have also shown an association between serum triglycerides and IHD A larger proportion of persons with elevated serum triglyceride values has been reported among male (1 30 43 44) and female infarction patients (2 43 44) than among controls In prospective studies too elevated triglyceride levels have been associated with an increased risk of IHD and/or MI (6 37 86) Wilhelmsen et al (86) found however that serum triglycerides did not improve predictive ability with respect to risk when the cholesterol value was known When multivariate analysis of triglycerides was performed instead of cholesterol the predictive ability was much lower

It has been discussed since long whether or not demonstrated risk factors are also of etiological importance for the development of coronary heart disease and MI It is possible that some of the risk factors are of etiological importance while others are only associated with increased risk of the disease The cause of a disease is always a complex problem It may be of value to analyse a suspected causal factor from two points of view—is it necessary for the development of the disease and is it alone sufficient to cause the disease The risk factors for MI so far studied are probably neither necessary nor sufficient Definite evidence of etiological significance has not so far been obtained for any of the risk factors for MI with the possible exception of the hereditary form of hypercholesterolaemia type II A which occurs in the Muller Harbitz syndrome Smoking is an example of a risk factor for MI the etiological significance of which has been much debated It has been asserted that smokers exhibit a special personality pattern considered to predispose to MI (25) and that they are more often known to be intemperate than others (24 86) On the other hand the results of prospective studies in which multivariate analysis has been performed indicate that smoking per se is a risk factor It has been shown that the variable smoking increases the information beyond that obtained from other variables including intemperance thus improving the predictive capacity of the multiple risk function (86) The findings that increasing tobacco consumption increases the risk and that the risk is less in those who stop smoking than in smokers also suggest that smoking is of etiological importance We have found that the prognosis was better in those who stopped smoking after MI than in those who continued to smoke which also supports the assumption of a causal relationship (88) Several possible theories concerning the pathogenetic mechanisms with respect to smoking and MI have also been suggested which further strengthen the suspicion that smoking is of etiological importance The aspects discussed here with respect to smoking can also be applied to several other risk factors for assessment of possible etiological importance

In order to prove that a risk factor or a group of risk factors is of etiological importance a controlled prospective study with an intervention group and a control group is required If such a study would show that reduction or elimination of the risk factor or factors concerned leads to a reduced incidence in the intervention group compared with the control group it ought to be possible to ascribe etiological importance to the factor Primary preventive studies of this type are in progress (85)

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Chronic Myocardial Disease

I Clinical Picture Related to Long term Prognosis

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ABSTRACT The prognosis in chronic myocardial disease is not well defined, partly because of a wide spectrum of clinical courses, and partly because of relatively short observation periods This paper describes 106 patients followed for 2–12 years Development or worsening of symptoms after intercurrent infections was associated with a more severe outlook than an insidious debut The ability to develop myocardial hypertrophy appeared to be an important factor in deciding the prognosis Pump failure was the cause of death in 80% of the patients, while 16% died suddenly A favourable course was often noted in patients with ECG signs of left ventricular hypertrophy This was also the case in patients who developed systemic hypertension The presence of low voltage, especially in combination with left atrial enlargement, was associated with a malignant development

This paper presents a clinical study of patients with chronic myocardial disease Some of the patients have been reported previously from this department (19) and the present work is an extension and long term follow up of that study Haemodynamic findings are presented in a subsequent paper (14)

MATERIAL

During a 10-year period (1962–72) 138 patients with chronic myocardial disease (hypertrophic obstructive cardiomyopathy not included) were admitted to our hospital Twelve of them had sarcoid heart disease and will be reported separately

At follow-up 9 patients could not be traced and in 11 the observation time was less than two years Both these groups were excluded leaving 106 patients (30 women and 76 men) for analysis The age distribution is seen in Fig 1 All patients had signs of myocardial disease in the absence of hypertensive valvular or coronary heart disease The diagnosis was confirmed by right and left heart catheterization and/or autopsy in all Selective coronary angiography was done in all except 10 patients the latter had symptoms before the age of 20 and significant coronary artery disease was assumed to be absent Autopsy was performed in 36 of the 50 patients who died None of them had coronary artery disease of notable degree Neither were signs of coronary artery disease found on any patient s coronary arteriograms

The cause of the disease was unknown in most of the patients (Table I) The group previous infection included 15 cases with respiratory infection one or a few weeks prior to onset of symptoms Four patients developed cardiac symptoms or signs within months to one year after debut of acute hepatitis Three of them were still recovering Two patients had diphtheria and one scarlet fever with symptoms of heart disease closely following Two other patients had had diphtheria years previously Three patients had initially acute myopericarditis with clinically complete recovery in one and symptoms after 2 or 3 relapses in the other two

Primary amyloidosis was seen in 6 patients all of them had signs of other organ involvement as well (liver kidney tongue)

Only two patients were clearly alcoholic several patients had never tasted alcohol while most took it only occasionally

One patient had phaeochromocytoma which was not diagnosed before she died in heart failure without recorded hypertension after a few months illness

RESULTS

Symptoms and signs

Dyspnoea on exertion was the first complaint in nearly half of the patients (Table II) and was later experienced by most of them (77%) Arrhythmia was the presenting symptom in nearly 30% and

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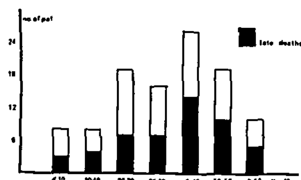


Fig 1 Age distribution at onset of symptoms or detection of disease

Table II *Symptoms and signs of chronic myocardial disease*

1st symptom/finding	
Dyspnoea on exertion	52
Arrhythmia	30
Asthenia	6
Chest pain	3
Cardiomegaly on X ray	7
All symptoms	
Dyspnoea on exertion	82
Arrhythmia	38
Asthenia	24
Chest pain	11
Syncope	4

often later the main symptom for years before dyspnoea and still years later heart failure ensued Asthenia especially on or after exertion was present in 23% and was the main symptom in most of them Chest pain was experienced by 10% in a few resembling angina pectoris but more often characterized by longer duration and often onset some time after exertion Syncope occurred only in patients with A V block In 7 patients the disease was discovered after routine chest X ray showing cardiomegaly

On first admission 31 patients had signs of left and right heart failure while 3 had left heart failure only During observation 22 more patients went into heart failure making a total of 56 of the 106 patients Biventricular failure was found in 52 iso left ventricular failure in 3 and isolated right cular failure in 1 (normal left ventricular pressures and angiogram)

Table III shows functional class at the first investigation later deaths and functional class at follow up Among most of the surviving patients the condition seems to have been rather stationary

Electrocardiograms

Arrhythmias and/or conduction disturbances usually atrial fibrillation and ventricular premature beats were recorded in 78 of the patients (Table IV) Atrial arrhythmias were seen in 53 of them Atrial fibrillation initially often paroxysmal was still paroxysmal in 2 patients at follow up Among patients with permanent atrial fibrillation electrical conversion was tried in 7 and was initially successful in 6 Relapses occurred in 4 while 2 maintained sinus rhythm with considerable clinical improvement The ventricular premature beats were frequent and persisted despite treatment for several years The patients with ventricular fibrillation were all in heart failure and none of them survived

Permanent pacemakers were implanted in 8 patients 6 of them had A V block 1 sinoatrial block and 1 slow atrial fibrillation One of them died later in heart failure and one of non-cardiac causes

ECG was normal in only one patient on both the first and the second admission the latter after 5 years known duration of disease In 6 patients the only abnormality on first admission was atrial fibril

Table I *Etiology of chronic myocardial disease in the 106 patients studied*

Unknown	57
Previous infection	27
Amyloidosis	6
Familial	5
Alcohol	2
LED	3
Rheumatoid arthritis	3
Muscular dystrophy	1
Scleroderma	1
Phaeochromocytoma	1

Table III *Functional class on admission and at follow up and deaths in between*

	No of pats	Functional class			
		I	II	III	IV
1st admission	106	34	32	12	28
Later dead	50	7	12	6	25
		27	20	6	3
2nd examination	56	23	20	9	4

Table IV *Arrhythmias*

Atrial fibrillation	38
Atrial flutter	3
Supraventricular tachycardia	9
Ventricular extrasystoles	18
Ventricular tachycardia	6
Ventricular fibrillation	3
Sinus bradycardia (<50)	7
S A block	7
A V block I	10
A V block III	6

lation On the second admission ECG was otherwise normal in only 3 of them

The changes in PQRS configuration are seen in Table V Patients with low voltage on the first examination and alive at follow up had unchanged ECG Another 3 patients had developed low voltage *during the observation period Signs of left ventricular* hypertrophy were unchanged in 10 increased in 8 and showed regression in 1 while 2 patients had developed left bundle branch block (LBBB) Four more patients had developed signs of left ventricular hypertrophy during the observation period Fourteen patients (13%) had an abnormal Q wave compatible with myocardial infarction in 2 or more leads At follow up this was present in another 2 patients In all of them selective coronary arteriography and/or autopsy showed normal or large coronary arteries without occlusions or narrowing At autopsy diffuse or patchy fibrosis of the myocardium was found One patient had a larger area of fibrosis in the anterolateral wall of the left ventricle ECG showing an abnormal Q wave in leads I aVL and V_4 V_6 Left atrial enlargement often pronounced was seen in one fourth of the patients Preexcitation was seen in 2 patients

ECG changes related to survival (and observation time) are also shown in Table V Patients with left ventricular hypertrophy fared best—only 5 of them died during the observation period and only one in heart failure Three of them died suddenly With low voltage LBBB and left atrial enlargement prognosis was not so good as 3/4 of the patients with these changes died after a mean observation time of 2–3 years Ten of 12 patients with both low voltage and left atrial enlargement died after a mean period of 1 5 years

Heart size

Heart volume on first admission as well as the number of later deaths in each group are shown in Fig 2 It is noted that heart size was normal in 20% of the patients In many patients it remained unchanged for several years although initially enlarged *When heart size was above 700 ml/m* mortality was increased But later changes in heart size were equally important in deciding the prognosis as there were 2 deaths among 20 patients with no change and 12 deaths among 32 patients with increasing heart size

Thromboembolism

In 20 patients the myocardial disease was complicated by embolism pulmonary in 5 (one had atrial fibrillation) and peripheral in 15 (8 had atrial fibrillation) Most of them had congestive heart failure In addition mural thrombi in one or both ventricles were found at autopsy in 9 of 35 patients

Pregnancy

Among the 30 women 6 became pregnant The pregnancies were associated with onset of or increase in symptoms In 5 of them signs or symptoms of

Table V *ECG findings in the 106 patients*

	1st admission	Mortality (%)	Observation period (y)	Duration of symptoms (y)
Low voltage	34	70	3 0	6 2
Left ventricular hypertrophy	23	22	7 7	14 0
LBBB	20	75	2 8	12 2
RBBB	11	36	5 3	14 3
Q II III aVF -6				
I aVF 6				
V_2 V 2				
V_4 V_6 3	14	64	4 2	15 8
Left atrial enlargement	24	70	2 4	7 4
Right+left enlargement	4			

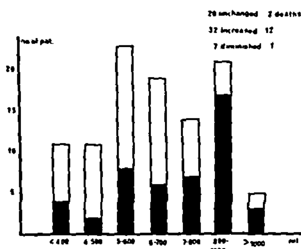


Fig 2 Heart size (ml/m²) at first examination ■=later deaths

heart disease had been present prior to the pregnancy The woman without known heart disease earlier developed heart failure in the last weeks of pregnancy She died in heart failure some weeks later and a bilateral phaeochromocytoma was found at autopsy The myocardium showed extensive necrosis and fibrosis and some hypertrophy Accordingly no cases of heart disease related solely to pregnancy were seen

Course

During the observation period 50 of the 106 patients died Forty died of congestive heart failure which was present on first admission in 23 while 17 were then in functional classes I–III Eight patients died suddenly They were all in functional classes I or II Two died of non-cardiac causes

Fig 3 shows known duration of disease in dead patients before death and in patients still alive About half of the deaths occurred within 5 years from onset of symptoms In one fourth the disease lasted for more than 10 years In 22 of the 56 patients still alive duration of disease was more than 15 years

Time of death related to onset of heart failure is seen in Fig 4 When heart failure had occurred few patients survived for more than 1–2 years

DISCUSSION

The observation period in this series was quite long (2–12 years) and disclosed a wide spectrum of severity of myocardial disease from early and persistent heart failure and death within a year or two to a relatively stable course showing only moderate deterioration during a period of 10 years or more When duration of symptoms prior to the first investigation is added myocardial disease may evidently be present in some patients for 20 years or more before death Often an intermediate course was observed with initial recovery from symptoms or heart failure for a few years and recurrence of heart failure often during or following an acute respiratory infection and then often persistent despite treatment This spectrum of myocardial disease has been emphasized by others (16) but there is still some uncertainty about the factors which influence the prognosis possibly partly due to the relatively short observation periods in many reports

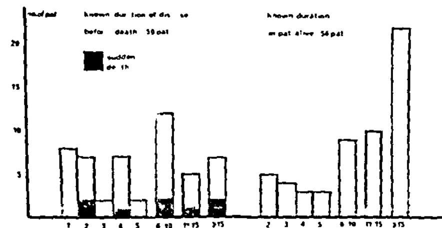


Fig 3 Duration of disease in patients who died later (left) and in patients alive (right)

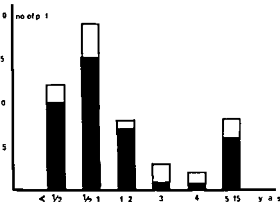


Fig 4 Duration of disease after first episode of congestive heart failure ■=deaths

The outcome seems generally to be determined by the degree of initial and/or continuing damage to the myocardium and perhaps by the degree of secondary hypertrophy as myocardial pump failure caused death in most of the present patients 80% while sudden death occurred in 16% This contrasts with a previous study (17) where 9 of 10 patients died suddenly this being related to the presence of frequent premature beats in 8 However in another study (11) the main cause of death was congestive heart failure with pulmonary embolism as an additional cause and only 4 of 35 patients died suddenly

An analysis of the present material reveals a number of points that are relevant to the prognosis Cardiomyopathies of unknown cause were not separated from those of known cause as their courses showed no distinct differences The patients with amyloidosis however may differ from others Five of these six died 2–8 years after development of symptoms The patient with the longest duration of the disease was the only one with hypertension A restrictive haemodynamic pattern similar to that seen in amyloidosis was also noted in a few others with myocardial disease of unknown cause

Development of chronic myocardial disease in 3 patients following acute myopericarditis has also been reported by others (5 18) and supports the theory of viral infection as a cause of cardiomyopathy In other patients heart symptoms were first noted shortly after a respiratory infection Some of them had antibody titers indicating past viral infection mostly Coxsackie B but in none of them were serological tests carried out early enough to establish a relationship between virus infection and myocardial disease Occurrence of cardiac symptoms following respiratory infection might represent an earlier myocardial disease becoming symptomatic The course of disease was notably more progressive—with early heart failure and death in heart failure within 1 to 4 years—in these patients than it was in those with a more insidious onset of symptoms and without known previous infections It was likewise notable that patients in a previously stable condition became worse often with intractable heart failure after respiratory infection

In a follow up study of patients with acute myocarditis Gerzen et al (7) found residual ECG changes in some but normal heart volumes and working capacities in all Relapses were seen in two patients however and a longer follow up would be of interest

In epidemic hepatitis ECG changes have been described and myocarditis has been observed in fatal cases (1) Three of our 4 patients who developed myocardial disease after hepatitis died later one suddenly (during strenuous exercise) after 8 years the other two from heart failure after 8 and 19 years respectively Autopsy in the latter two showed signs of chronic myocarditis with fibrosis hypertrophy and increase in lymphocytic cells One of these patients was almost without symptoms until the last months of her first pregnancy when she developed heart failure with worsening post partum and died 3 weeks later

Peripartum cardiomyopathy is regarded as a separate entity (3) of unknown cause and without prior cardiac disease but was not present in any of our six patients with symptoms during the last part of pregnancy or shortly after

The number of patients with alcoholic cardiomyopathy was very small compared with other studies showing percentages from 20 to 50 (8 10) The reason may be connected in some way with the referring policy as most patients initially came from other hospitals for further investigation Obtaining a history of alcoholism may be difficult but the patients were seen over many years and questioned repeatedly and thoroughly

Goodwin (8) noted a slightly better prognosis with hypertension which was present in 1/4 of his patients The mean duration of symptoms was 5 4 years compared with 3.3 years in those without hypertension Hypertension was seen

quently among the present patients (10%) but was also associated with a better prognosis Hypertension developed during the observation period in all the 11 patients 5 of them showing ECG signs of left ventricular hypertrophy The mean duration of disease was 11 years and 9 of the 11 patients are still alive It should be noted that most patients with ECG signs of left ventricular hypertrophy were normotensive

Systemic or pulmonary embolism is a well recognized complication of myocardial disease especially in patients with congestive heart failure The higher frequency in the present study (19%) compared with 10% reported by Hamby (11) may be due to a longer observation period

As shown in other studies the main symptoms of chronic myocardial disease were dyspnoea arrhythmias and fatigue Arrhythmia as the presenting problem was seen in almost 30% The occasional presence of cardiomegaly for years before symptoms has also been noted by others as has the occurrence of chest pain resembling angina pectoris in about 10% of patients (9 11)

Atrial arrhythmias were seen in 50% of the patients compared with one third in a report of 100 patients (11) and 22% in a compiled study of 631 patients (4) Frequent premature beats were present in 18% of our patients compared with 36% and 12% respectively in the two series mentioned The frequency of A V block was the same as in the compiled study 15% but complete A V block was more frequent in our study (6% versus 0 7%)

Sinus arrest was found by Hamby (11) in 3% compared with an incidence of sinoatrial block or sinus arrest of 7% in the present study or a possible incidence of sinus node disease in 13% if sinus bradycardia (heart rate < 50) is added

More relevant to prognosis was the PQRS configuration on ECG Flowers and Horan (4) in a review of 631 compiled patients with non familial non-obstructive myocardial disease found left ventricular enlargement as the most frequent abnormality The incidence of low voltage was not mentioned but in the present study it was the most frequent ECG finding 35% compared with 23% in Hamby s study (11) The incidence of left atrial enlargement was 38% in the study of Hamby compared with 27% in the present study and only 14% in the compiled study Previous studies do not mention the prognostic significance of left ventricular hypertrophy This finding was associated in the present study with a relatively good prognosis contrasting with the much worse prognosis of low voltage especially when this was combined with signs of left atrial enlargement ECG signs of left ventricular hypertrophy have been reported in 33-67% of patients with chronic myocardial disease (excluding patients with hypertrophic cardiomyopathy) (4 11 13) In the present series ECG signs of left ventricular hypertrophy were seen only in 24% The mortality during observation was much lower in these patients (20% versus 56% in patients without hypertrophy) Some authors (11 12) have suggested an early hypertrophic stage later progressing with dilatation and loss of voltage in ECG This was seen during observation in only one patient in the present series while several patients showed increased voltage and one patient even developed ECG signs of left ventricular hypertrophy after a period of heart failure years after the start of symptoms Q waves compatible with myocardial infarction in myocardial disease with normal coronary arteries have previously been reported (6 15 20) and were observed in 15% of our patients as against 10% in a previous study (11)

Bundle branch block was almost twice as frequent as in other studies (2 4 11) LBBB occurred more than twice as frequently as RBBB The mortality among patients with the former was high but much lower among those with the latter

CONCLUSION

It may be concluded that the following clinical features adversely affect the prognosis in chronic myocardial disease Onset or relapse of symptoms after intercurrent infection early congestive heart failure low voltage on ECG especially when combined with left atrial enlargement left bundle branch block and heart size above 700 ml/m² On the other hand the development of systemic hypertension and especially left ventricular hypertrophy on ECG were associated with a favourable prognosis

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Chronic Myocardial Disease

II Haemodynamic Findings Related to Long term Prognosis

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ABSTRACT Haemodynamic findings in 106 patients with chronic myocardial disease have been related to the course of the disease during a follow up period of 2–12 years *A high filling pressure especially when* combined with low cardiac output suggested a severe development The worst outlook was noted in patients who in addition had raised pulmonary arteriolar resistance On the other hand, a low filling pressure even if cardiac output was reduced, was generally associated with a more benign course An increase in left ventricular wall thickness as determined angiographically suggested a better outlook than normal wall thickness

This paper presents haemodynamic findings and their significance for the prognosis in 106 patients with chronic myocardial disease The clinical data have been reported and discussed in a preceding paper (6)

METHODS

Heart catheterization was done as previously described (11) The reference level for pressure measurements was the anterior axillary line in the fourth intercostal space Cardiac output was mostly measured by the Fick method and occasionally by the dye dilution method using Cardiogreen When exercise testing was done during heart catheterization a load of 150/300 kpm was used for 6–10 min Left ventricular cineangiograms were taken on 35 mm film in the right anterior oblique projection with the catheter introduced percutaneously from the femoral artery Ejection fraction was calculated from single plane cine angiograms (8 10) using the area of the left ventricular cavity measured by planimetry and the length to calculate the short axis Wall thickness was measured on the free left ventricular wall (9)

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RESULTS

Fig 1 shows right heart and left ventricular end diastolic pressures as well as cardiac index at the first examination The values are shown separately for patients still alive and for those who died later More patients in the latter group had raised right heart pressures otherwise there was no clear distinction between the two groups Low or normal pressures at rest were seen in 43% of the patients In patients with a mean pulmonary wedge pressure of less than 10 mmHg the mortality during the observation period was 16% as against 56% in those with higher pressures

Signs of restrictive cardiac disease with diastolic pressure curves from the ventricles showing early diastolic dip and raised end diastolic pressure were seen in the patients with amyloid heart disease but also in 4 others Two of the latter died Autopsy showed pronounced fibrosis with only slight to moderate dilatation of the ventricles The other two are alive and there is no suggestion of amyloidosis carcinoid heart disease or endomyocardial fibrosis Their angiograms showed slightly dilated but stiff poorly contracting ventricles

Cardiac index was 2 2 l or below in 29 patients in a few patients it was very low Some of these had congestive heart failure others had no signs of failure but had low exercise tolerance or pronounced asthenia

During exercise a pathological increase in pressure was seen in some of 11 patients (Fig 2) Increased but less than normal cardiac index during exercise was seen in all None of them showed an increase in stroke volume the increase in cardiac index being solely due to an increase in heart rate

Twelve patients were subjected to repeated catheterization after 3–12 years (Fig 3) In most of

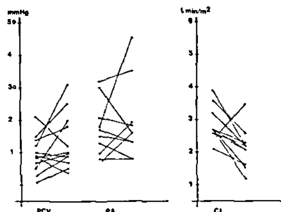


Fig 3 Right heart pressures and CI at first and second examination in 12 patients Mean interval 8 years (range 2-1?) Abbreviations as in Fig 1

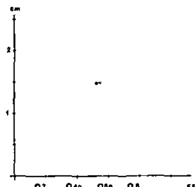


Fig 5 Ejection fraction related to wall thickness O=patients without congestive heart failure ×=patients with previous congestive heart failure ▲=patients in congestive heart failure ●=patients who died later

most of those with high pressures are dead The former included many with a long history presenting fatigue as the main symptom with a stationary or rather slowly progressing course

Among patients who had a cardiac index above 2 5–2 6 there was no such clear separation Most patients with a restrictive pattern on pressure recordings and only moderately dilated ventricles and a normal cardiac index were found in this group while patients with a low cardiac index had more dilated ventricles

When ejection fraction and left ventricular end-diastolic pressure were combined most patients who died had LVEDP of 20 mmHg or above and an ejection fraction below 0 35 (Fig 4) The two exceptions both died suddenly ECG in one of them two days prior to death had shown RBBB combined with left posterior hemiblock

When the patients were divided according to their left ventricular end diastolic and/or pulmonary wedge pressure there were 43 with normal and 50 with raised pressures (Table 1) The mortality in patients with normal pressures was 28% and in patients with raised pressures 50% during a mean observation period of 5 4 and 4 4 years respectively Mean duration of disease was slightly shorter in the latter group (10 3 against 13 2 years) This was due to a shorter duration in the patients who died

Among patients with normal pressures the duration of disease ejection fraction cardiac index and pulmonary arterial resistance were similar in survivors and in those who died while among patients with elevated pressures those who died later had a lower cardiac index and a higher pulmonary arteriolar resistance th in those still alive

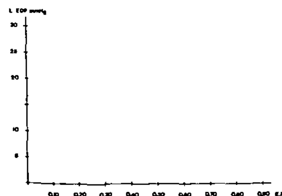


Fig 4 Ejection fraction related to left ventricular end diastolic pressure ●=patients who died later ×=patients still alive

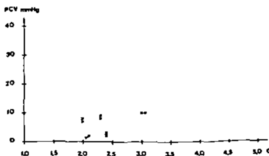


Fig 6 Pulmonary capillary venous pressure related to cardiac index ×=patients still alive ●=patients who died later

Table I *Haemodynamic data in patients with chronic myocardial disease*

Group I = patients with left ventricular diastolic pressure below 12 mmHg and/or mean pulmonary wedge pressure below 9 mmHg group II = patients with pressures above these values

	Group I			Group II		
	Total	Alive	Dead	Total	Alive	Dead
No of patients	43	72%	28%	50	50%	50%
Mean observation time (y)	5 4	6 4	2 8	4 4	6 0	2 9
Mean duration of disease (y)	13 2	14 0	10 8	10 3	13 7	6 8
Ejection fraction		0 51	0 40		0 46	0 20
Cardiac index		2 7	3 1		2 6	2 3
Pulmonary vascular resistance		123	152		133	247

DISCUSSION

Cardiomyopathy is usually associated with signs of left ventricular involvement (except in patients with endomyocardial fibrosis) right ventricular failure being secondary to failure of the left ventricle However isolated right ventricular failure has also been described (7 13) In the present study 4 of the 106 patients showed predominantly right ventricular involvement In one of them no signs of left ventricular disease could be detected

Several haemodynamic studies of patients with myocardial disease have been reported (1 2 4 7 8 12) The findings vary from only barely detectable abnormalities in cardiac function sometimes only during exercise to severely raised ventricular filling pressure dilated ventricle low cardiac index low ejection fraction and raised pulmonary artery wedge pressure In some patients a specific feature has been the combination of dilated ventricles with or normal diastolic pressure (8)

Several ways have been tried for grouping patients with myocardial disease according to haemodynamic findings Gould et al (2) described 3 groups depending on diastolic pressures and cardiac index 1) An early stage with normal pressures and cardiac index at rest (but reduced ejection fraction) 2) A later stage with two different pathways—either raised pressures and maintained cardiac index or normal pressures with low cardiac index 3) A late stage with raised pressures and low cardiac index Others (1 7) have used the left ventricular angiogram to describe stage or type of myocardial involvement while Hamby et al (4) divided their patients in two groups depending on normal or raised filling pressure Data from the present study support the suggestion (2 12) of different patterns in the progression of myocardial disease as repeat catheterization showed raised pressures with only moderate reduction of cardiac output in some and unchanged or even lower pressures with a large reduction of cardiac output in others

When our patients were divided into two groups —those with normal and those with raised left ventricular diastolic pressures—the mortality in the former was 28% against 50% in the latter These figures correspond well to 21 and 54 reported by Hamby and Raia (5) However the observation time in our study was much longer (2–12 years mean 6 versus 2–60 months) indicating a comparatively more favourable outlook This might be due to differences in etiology (the frequency of alcoholic cardiomyopathy was high in Hamby and Raia s series and very low in the present material) or to differences in progression of disease even after a stage of increased pressure has been reached

Due to the relatively long follow up period it seems justified to analyse the present material for the combination of haemodynamic data which could best predict the prognosis Low pressures even when combined with a low cardiac index were often associated with a relatively long survival High filling pressures alone indicated a somewhat higher mortality even when combined with a normal cardiac index Most of the patients who died suddenly had this combination The mortality was definitely even higher when high filling pressures were combined with low cardiac index/ejection fraction and especially when a high pulmonary arteriolar resistance was present as well (Table I and Fig 6) An increased left ventricular wall thickness appeared to be associated with a more favourable outlook than normal wall thickness This agrees with the findings in the clinical study showing a better prognosis in patients with left ventricu

lar hypertrophy on ECG than in patients without The degree of left ventricular hypertrophy may thus be one of the factors deciding the prognosis in chronic myocardial disease

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Table I *Blood glucose concentrations and serum insulin values at different times after an oral glucose load as well as some other parameters in individuals with different Lp phenotype (mean ±S D)*

All Lp(a−) individuals lacked pre β_1-lipoprotein

	Lp(a+) (*n*=14)	Lp(a−) (*n*=16)	*t*	*p*
Weight (kg)	78 2± 7 8	77 1± 9 5	0 34	N S
Height (cm)	173 6± 6 0	175 8± 5 6	−1 03	N S
Blood glucose (mg/100 ml)				
0 min	94 4± 8 4	96 2±12 2	−0 45	N S
60 min	167 4±28 7	175 0±65 3	−0 40	N S
120 min	91 6±19 0	108 7±48 1	−1 24	N S
Δglucose				
60 min	72 9±29 6	78 8±64 6	−0 31	N S
Insulin (μU/ml)				
Fasting	13 7± 3 0	16 0± 8 8	−0 93	N S
60 min	64 7±26 2	81 9±49 8	−1 16	N S
120 min	20 1± 9 5	35 6±27 1	−2 03	N S (~0 05)
Δinsulin				
60 min	51 0±25 2	65 9±42 6	−1 15	N S
120 min	6 6± 9 3	19 6±21 1	−2 13	<0 05
Triglycerides (mmol/l)	2 6±1 4	2 4± 1 1	0 38	N S
Cholesterol (mg/100 ml)	310 1±46 3	273 1±44 6	2 23	<0 05

at 7–7 30 a m In all 16 individuals previously typed as Lp(a−) and 14 previously typed as Lp(a+) (8) were studied All the Lp(a−) subjects were chosen at random among those who had been classified as pre β_1− The 14 Lp(a+) individuals comprised 10 males who had exhibited a particularly prominent pre β_1-lipoprotein fraction belonging to the 1 050–1 080 density class at the previous investigation The remaining 4 Lp(a+) subjects had been ored as pre β_1 −

OGTT was performed by administering 30 g glucose/m² BSA as a 10% glucose solution The total volume was consumed during a 5-min period

Fasting samples including specimens for glucose insulin total cholesterol and triglyceride (TG) determinations were drawn about 5 min before glucose was administered The timing of all blood samples during the OGTT started at the beginning of the glucose ingestion Samples were obtained for glucose measurements at 30 45 60 75 90 120 150 and 180 min and for insulin determinations at 60 and 120 min

Samples for blood glucose determination were analyzed at once employing a manual modification of the hexokinase method (18) and using 44 7 μl blood in 2 ml of isotonic sodium chloride solution with 0 2% sodium fluoride

Immunoreactive insulin (IRI) was measured in duplicate in serum which had been stored at −20°C until the time of analysis using a Phadebas insulin test kit for radioimmunoassay (Pharmacia Uppsala Sweden)

Total cholesterol and TG were determined as previously described (7 11) using a Technicon AutoAnalyzer I (Technicon Instruments Corporation Tarrytown New York)

Lipoprotein electrophoresis was performed in 0 5% agarose as described previously (7 13)

Desirable body weight was obtained from the tables published in Documenta Geigy (14) For a given height the criterion of obesity was an actual weight exceeding 110% of the upper range for "medium frame

The differences in insulin or glucose values at 60 or 120 min compared to the values prior to the start of OGTT are referred to as Δinsulin and Δglucose

Differences between means were analyzed by the *t* test

RESULTS

Classification of the samples with respect to presence or absence of pre β_1 lipoprotein agreed completely with the previous findings on these samples The migration of the pre β_1 lipoprotein fraction relative to that of albumin was strikingly constant with the 10 samples which were positive for Lp(a) antigen as well as pre β_1 lipoprotein

Blood glucose concentrations and serum insulin values at the start and at 60 and 120 min of the OGTT as well as some other parameters are shown in Table I for males with different Lp types No significant differences in mean body weight or height were found between the two groups More than 10% overweight was found in 57% of the Lp(a+) individuals and in 50% of the Lp(a−) individuals No difference in mean blood glucose was found at any time during the OGTT One of the Lp(a−) individuals (no 22) had a normal blood sugar after a 12 hour s fast but a rise to 357 mg/100 ml during 60 min of OGTT glucosuria and a slow return to normal values He was considered to have latent diabetes When this individual was excluded the blood glucose curves during the OGTT were very similar between Lp(a+) and Lp(a−) individuals (Fig 1) and there was no significant difference with respect to Δglucose levels at 60 min (Table I)

The difference in mean insulin values was almost significant at 120 min with a tendency towards a lower mean value in the Lp(a+) group A difference in mean Δinsulin values at 120 min during OGTT was found with a higher mean value in the Lp(a−) group

No difference in TG was found between the two groups Mean total cholesterol was however higher in the Lp(a+) than in the Lp(a−) group The same trends were found when the pre β_1−/Lp(a)

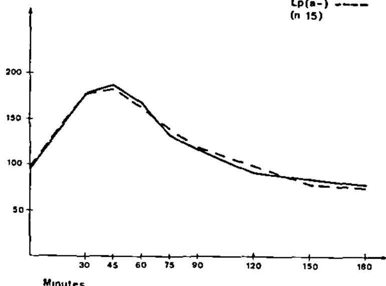


Fig 1 Blood glucose during 180 min after an oral glucose load The continuous curve shows mean values for 14 Lp(a+) males and the dashed curve mean values for 15 Lp(a−) males Individual no 22 who had a latent diabetes was excluded from the latter group

group was compared with only those 10 Lp(a+) males who had been scored as pre β_1+ (Table II)

The subjects were also divided into two groups according to TG values (Table III) Those with the higher TG values also had a higher mean value of total cholesterol No difference was found in mean values for blood glucose The insulin mean values after a 12 hour s fast and at 60 and 120 min during the OGTT were however higher in the group with high TG values

As can be seen from Tables I and II the S D appeared to be higher for insulin and Δinsulin values in the pre β_1−/Lp(a−) group than in the pre β_1+ and Lp(a+) groups

A further analysis of these data showed that although there was no difference in TG mean levels between Lp(a+) and Lp(a−) individuals as shown in Table I the six Lp(a−) individuals with the highest insulin levels at 60 min during the OGTT had a TG mean level of 3 3 mmol/l whereas the six Lp(a−) individuals with the lowest insulin levels after 60 min had a TG mean level of 2 0 mmol/l (p<0 05)

A regression analysis showed a significant correlation between fasting TG level and insulin value at 60 and 120 min during OGTT in individuals who were classified as pre β_1−/Lp(a−) (r=0 57 p<0 05) (Fig 2) One subject (no 27) had an abnormal fasting blood glucose value and a negative Δglucose at 60 min of OGTT When this abnormally reacting individual was excluded the correlation coefficient between TG and insulin levels at 60 min of OGTT in the 15 Lp(a−) individuals was 0 76 (Fig 2)

Table II *Blood glucose concentrations and serum insulin values after exclusion of four Lp(a+) individuals without detectable pre β_1-lipoprotein (mean ±S D)*

	Pre β_1+/ Lp(a+) (n=10)	Pre β_1−/ Lp(a−) (n=16)	t	p
Weight (kg)	78 5± 7 8	77 1± 9 5	0 38	N S
Height (cm)	173 8± 6 2	175 8± 5 6	−0 83	N S
Blood glucose (mg/100 ml)				
0 min	93 2± 8 3	96 2+12 2	−0 68	N S
60 min	163 2±27 7	175 0±65 3	−0 54	N S
120 min	87 3±15 8	108 7±48 1	−1 35	N S
Δglucose				
60 min	70 0±26 3	78 8±64 6	−0 24	N S
Insulin (μU/ml)				
Fasting	13 5± 3 2	16 0± 8 8	−0 86	N S
60 min	59 9±17 1	81 9+49 8	−1 34	N S
120 min	17 3± 7 2	35 6±27 1	−2 08	<0 05
Δinsulin				
60 min	46 4±16 0	65 9+42 6	−1 38	N S
120 min	4 0± 6 9	19 6±21 1	−2 25	<0 05
Triglycerides (mmol/l)	2 6± 1 5	2 4± 1 1	0 41	N S
Cholesterol (mg/100 ml)	318 9±51 3	273 1±44 6	2 40	<0 05

Table III. *Blood glucose concentrations and serum insulin values at different times after an oral glucose load as well as some other parameters in individuals with triglyceride values above and equal to or below 2.0 mmol/l (mean ± S.D.)*

	TG >2.0 *mmol/l* (*n* = 16)	TG ≤2.0 *mmol/l* (*n* = 14)	*t*	*p*
Weight (kg)	79.9 ± 7.5	75.0 ± 9.3	1.58	N.S.
Height (cm)	175.1 ± 4.6	174.3 ± 7.1	0.39	N.S.
Blood glucose (mg/100 ml)				
0 min	84.9 ± 32.7	91.1 ± 7.9	−0.70	N.S.
60 min	168.3 ± 43.2	175.0 ± 60.0	−0.36	N.S.
120 min	101.9 ± 23.0	99.4 ± 50.8	0.17	N.S.
Δglucose				
60 min	69.2 ± 45.1	83.9 ± 59.5	−0.79	N.S.
Insulin (μU/ml)				
Fasting	17.6 ± 7.7	11.9 ± 3.8	2.49	<0.02
60 min	87.6 ± 45.0	58.2 ± 29.6	2.08	<0.05
120 min	36.6 ± 24.3	19.1 ± 14.8	2.34	<0.05
Δinsulin				
60 min	70.1 ± 38.6	44.2 ± 30.7	2.01	N.S. (≈0.05)
120 min	19.0 ± 19.6	7.3 ± 13.4	1.88	N.S.
Triglycerides (mmol/l)	3.4 ± 0.9	1.5 ± 0.3	7.29	<0.001
Cholesterol (mg/100 ml)	309.3 ± 41.3	268.7 ± 48.0	2.49	<0.02

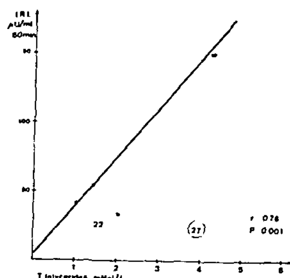


Fig. 2. Correlation between serum IRI 60 min after an oral glucose load and serum TG concentration after a 12 hours fast in 15 Lp(a−) individuals. One individual (no. 27) indicated in the figure was excluded from the statistical test on the basis of an abnormal fasting blood glucose value.

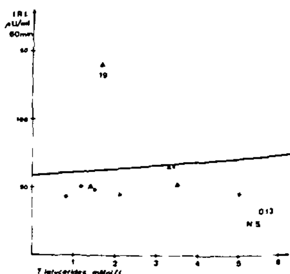


Fig. 3. Correlation between serum IRI 60 min after an oral glucose load and serum TG concentration after a 12 hours fast in 14 Lp(a+) individuals, 4 of whom were negative with respect to pre β_1 lipoprotein (▲).

No significant correlation between TG and insulin levels at 60 min of OGTT was found in pre β_1 positive or Lp(a+) subjects (Fig. 3). Subject 19 who was Lp(a+) but pre β_1− was the only one typed as Lp(a+) very weak. Exclusion of this individual did not significantly affect the outcome of the correlation analysis.

A significant correlation was also found between TG and insulin values at 120 min of OGTT in the Lp(a−) individuals ($r = 0.54$, $p < 0.05$) but not in the Lp(a+) subjects ($r = 0.26$).

Fig. 4 shows the regression line between fasting TG value and Δinsulin at 60 min during OGTT in Lp(a−) subjects (no. 27 excluded from the calculation of r). The correlation was significant (and remained so ($r = 0.55$, $p < 0.05$) even if individual no. 27 was included).

No significant correlation between TG value and Δinsulin at 60 min of OGTT was, however, found among the *pre β_1+ and Lp(a+) individuals (Fig. 5)* (even if subject no. 19 was excluded).

Fig. 6 shows the regression line for Δglucose and Δinsulin at 60 min of OGTT for the 14 Lp(a+) subjects. The correlation coefficient between Δglu*cose and Δinsulin at 60 min during OGTT* was significant even if the only individual typed as very weak Lp(a+) (no. 19) was excluded ($r = 0.81$, $p < 0.001$). There was even a significant correlation between blood glucose at 60 min and insulin levels

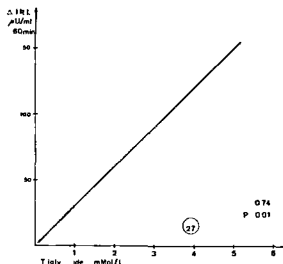


Fig 4 Correlation between Δserum IRI 60 min after an oral glucose load and serum TG concentration after a 12 hour's fast in 15 Lp(a−) individuals One individual (no 27) indicated in the figure was excluded from the statistical test on the basis of an abnormal fasting blood glucose value

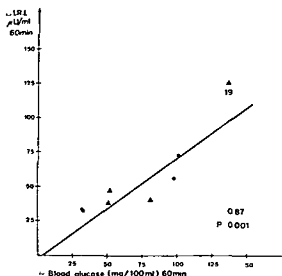


Fig 6 Correlation between Δserum IRI and Δblood glucose 60 min after an oral glucose load in 14 Lp(a+) individuals 4 of whom were negative with respect to pre β_1 lipoprotein (▲)

at 60 min during OGTT in the 14 Lp(a+) individuals (r=0 83 p<0 001)

No significant correlation was *found between* Δglucose and Δinsulin at 60 min during OGTT among the 16 Lp(a−) individuals (Fig 7) This was the case even if individual no 22 who had latent diabetes and no 27 who had a high fasting glucose level were excluded (r=0 34) There was no *significant correlation between blood glucose and* insulin levels at 60 min during OGTT in the 16 Lp(a−) individuals (r=0 10)

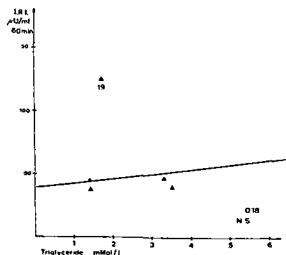


Fig 5 Correlation between Δserum IRI 60 min after an oral glucose load and serum TG concentration after a 12 hour s fast in 14 Lp(a+) individuals 4 of whom were negative with respect to pre β_1 lipoprotein (▲)

DISCUSSION

According to the theory of lipoprotein families the plasma lipoprotein system consists of free and as*sociated forms of lipoprotein species characterized* by their apolipoproteins (1) In very low density lipoprotein (VLDL) the lipoprotein families are complexed with triglycerides It has been established (20) that VLDL is a heterogenous mixture of lipoprotein subpopulations or species differing in protein composition One of the VLDL proteins is a co factor for TG hydrolysis by lipoprotein lipase but some of the VLDL species seem to have little or none of this protein (20) An alternative pathway for VLDL TG metabolism has been suggested probably by another enzyme system (20)

Lipoprotein lipase acts mainly in the capillary endothelium of adipose tissue and skeletal muscle but may also be present in the arterial wall Heparin has been suggested to act as a bridge linking VLDL and lipoprotein lipase to the intimal surface (22) While adsorbed the TGs are mainly metabolized

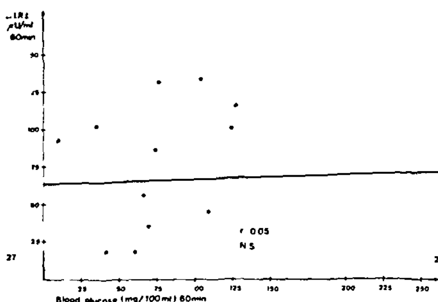


Fig 7 Correlation between Δserum IRI and Δblood glucose 60 min after an oral glucose load in 16 Lp(a−) individuals

and VLDL is transformed at least in part to *cholesterol rich low density lipoprotein* (17)

The comparatively high content in the Lp(a) lipoprotein of sialic acid (15) a component known to occupy peripheral positions on cell surface receptors (19) and the high content of mono- and diglycerides reported (21) may suggest a difference between Lp(a+) and Lp(a−) individuals with respect to an interaction between soluble lipoprotein and cell membranes The present findings may also suggest a different interference with the insulin receptor function (6)

The insulin response to an oral glucose load is mediated through a complicated process involving many factors and hormones However glucose seems to be the main stimulator for insulin release As the mean blood glucose values were the same during the OGTT in Lp(a+) and Lp(a−) individuals (Fig 1) it seems reasonable to assume that the insulin release is regulated mainly in response to the blood glucose values in all individuals

The observed higher mean level of insulin in individuals with high TG levels after a 12 hours fast as well as at 60 and 120 min during OGTT compared to those with normal triglyceride values is in agreement with findings by other authors (16)

The differences between the correlation coefficients in the Lp(a+) as compared with the Lp(a−) group (Figs 2–7) are impressive The significance of this difference is a critical point in the interpretation of the present data Therefore the hypothesis that the two sample values of *r* are drawn at random from the same population was tested for each of the three pairs of *r* values given in Figs 2–7 This was done by converting each *r* to *z* and testing the significance of the difference between the two *z*'s The following results emerged in comparison between *r* values in Figs 2 and 3 $0.025<p<0.05$ in Figs 4 and 5 $0.05<p<0.10$ in Figs 6 and 7 $0.001<p<0.005$ Thus the hypothesis has to be rejected for two of the three comparisons and we must conclude that the *r* values are drawn from different subpopulations

If confirmed the observed difference between Lp(a+) and Lp(a−) individuals with respect to a correlation between fasting TG level and insulin response during OGTT may be of considerable interest We find the possible significance of this phenomenon for the association between presence of Lp(a) lipoprotein and atherosclerotic heart disease (5 7 12) particularly intriguing

The present findings clearly support the view that the Lp(a) testing and the pre β_1 lipoprotein classification with the methods used separate two subpopulations with different genetically determined characteristics

ACKNOWLEDGEMENTS

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The Effect of Antilipolytic Agents on Cyclic AMP, Free Fatty Acid and Total Catecholamine Concentrations in Plasma

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ABSTRACT Plasma concentrations of adenosine 3 5 cyclic monophosphate (cyclic AMP) and free fatty acids have been measured in 15 patients with acute myocardial infarction and in 6 dogs given infusions of isoprenaline Plasma total catecholamines were also estimated in the patients Inhibition of adipose tissue lipolysis with a nicotinic acid analogue did not decrease plasma cyclic AMP concentrations either in the patients or when elevated in the dogs thus suggesting that this tissue is not a major source of the nucleotide in plasma

Intravenous isoprenaline given to healthy men results in an increase in the plasma concentration of adenosine 3 5 cyclic monophosphate (cyclic AMP) (1) The major source of this increased extracellular cyclic AMP has not been identified

Although the liver is a contributor (6) the i v injection of isoprenaline to hepatectomized rats results in a large increase in plasma nucleotide concentrations suggesting that extrahepatic tissues sensitive to catecholamine stimulation are also important sources (11) Since the rate of adipose tissue lipolysis is mediated by the intracellular concentration of cyclic AMP (2) adipose tissue might be expected to release the nucleotide into plasma In rats this is apparently not so For example in isolated rat adipose tissue pieces an isoprenaline stimulated increase in the rate of lipolysis is only accompanied by an increased release of nucleotide if the phosphodiesterase inhibitor theophylline is present in the incubation medium (15) Further in functionally hepatectomized rats an isoprenaline stimulated increase in plasma cyclic AMP concentrations is not affected by inhibition of adipose tissue lipolysis with nicotinic acid (11)

Adipose tissue constitutes a large part of the body weight in man and since it has recently been suggested that measurements of extracellular cyclic AMP concentrations may be useful in the diagnosis of some endocrine disorders (8) we have investigated the possibility that adipose tissue contributes to plasma cyclic AMP concentrations in humans

We describe serial plasma cyclic AMP measurements in patients with acute myocardial infarction (AMI) and the effect on these of antilipolytic treatment (9) using a nicotinic acid analogue (NAA) Since plasma cyclic AMP concentrations were not increased above the reference range in the patients studied the effects of nicotinic acid on plasma cyclic AMP were also investigated in six dogs given i v infusions of isoprenaline to increase cyclic AMP above basal concentrations

PATIENTS AND METHODS

The 34 patients studied were admitted to a Coronary Care Unit with suspected AMI All demonstrated 1) severe precordial pain for less than 12 hours 2) ECG evidence of infarction sufficient to warrant classification into Minnesota Code groups 1 1 or 1 2 3) increased serum creatine kinase activity 4) a clear time of onset of symptoms Differences in clinical severity between the two Minnesota Code groups were reduced by excluding patients with cardiogenic shock or overt cardiac failure Patients taking antilipolytic or adrenergic blocking agents patients

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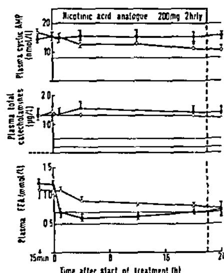


Fig 1 Effect of a nicotinic acid analogue on the plasma concentrations of cyclic AMP total catecholamines and FFA in patients with AMI given NAA (-●-) or placebo (-O-) Each point is the mean concentration ±1 S E The shaded areas indicate normal ranges

with diabetes mellitus hypothyroidism treated with thyroxine or hypertension treated with methyldopa were also excluded The patients were included in a double blind clinical trial of the effectiveness of a known antilipolytic agent in reducing the incidence of ventricular arrhythmias (9 10) and random numbers were used for allocation to treatment with NAA or placebo The mean age and sex of the groups and the median times of admission were as expected for the Coronary Care Unit

The study was passed by the ethics committee of this hospital and informed consent for administration of the AA (5 fluoro 3 hydroxymethyl pyridine hydrochloride) blood sampling was given by all 34 patients One psule of 200 mg NAA (15 patients) or an identical acebo (19 patients) was given every 2 hours for 22 hours starting 15 min after the first blood sample had been taken A blood sample was taken 15 min before and when the first capsule was given and at 1 4 12 20 and 24 hours During the study morphine diazepam digoxin diuretics and other drugs were given to patients as indicated but antiarrhythmic drugs were given only when a serious ventricular arrhythmia had been observed Few of the patients ate any food during the period of the study

In the second part of the study 6 mongrel dogs (15–23 kg) were studied after a fast of 12–16 hours Anaesthesia was initiated with i v sodium pentobarbital (25 mg/kg b wt) and maintained by further i v injections (30–40 mg) Arterial blood was sampled through a catheter inserted into a femoral artery and kept patent with sodium chloride (0 9% w/v) After drawing a basal blood sample isoprenaline (0 2 µg/kg/min) was infused into a femoral vein and a further blood sample was taken 10 min later The isoprenaline infusion was then stopped and after 30 min a new basal blood sample was taken Nicotinic acid (8–10 mg/min) was infused and blood was taken 15 min later The infusion of isoprenaline was then resumed as before and a further blood sample was drawn after 10 min of the combined infusion of isoprenaline and nicotinic acid

A protein binding assay was used to measure plasma cyclic AMP (11) a fluorescent trihydroxyindole method for plasma total catecholamines (4) and the Trout modification of the Dole titration method for plasma FFA (13) The reference range for plasma cyclic AMP concentrations obtained in 18 subjects without AMI was 9 0–22 3 nmol/l (mean 13 0 S D 3 5) (12) The range for plasma total catecholamines was 0 2–0 5 µg/l and for plasma FFA 0 4–0 8 mmol/l Statistical analysis was performed using the paired Wilcoxon and Mann Whitney *U* tests (5)

RESULTS

There was no significant difference in plasma concentrations of cyclic AMP between either of the groups of patients with AMI before treatment or 4 hours later (Fig 1 top) Neither was there any significant difference between initial values in these groups and values in the 18 subjects without AMI While plasma cyclic AMP concentrations in the NAA treated group showed no variation during the study plasma nucleotide concentrations in the placebo group fell with time Twenty hours and 24 hours after the start of treatment they were significantly lower than both values before therapy ($p<0\ 01$ $p<0\ 01$) and corresponding values in the NAA treated group ($p<0\ 05$ $p<0\ 01$)

Plasma total catecholamine concentrations were significantly elevated above normal values (0 2–0 5 µg/l) and were not different in the NAA treated and placebo groups neither showed any variation with time (Fig 1 middle)

The changes in plasma FFA concentrations are shown lowest in Fig 1 Before treatment plasma concentrations in the two groups were similar and elevated above the normal range One hour after starting treatment plasma FFA concentrations in the NAA treated group were significantly reduced ($p<0\ 01$) compared with the placebo group and this reduction was maintained at 4 hours ($p<0\ 01$) and 12 hours ($p<0\ 01$) By 20 and 24 hours plasma concentrations in the placebo group had fallen so that there was no significant difference between values in the two groups

Results from the anaesthetized dogs are given in Table I which shows basal cyclic AMP and FFA concentrations in arterial plasma

As expected the isoprenaline infusion resulted in significantly increased concentrations of cyclic AMP ($p<0\ 002$) and FFA ($p<0\ 002$) Infusion of

Table I *Effects of isoprenaline and nicotinic acid on plasma cyclic AMP and FFA concentrations in 6 anaesthetized dogs (mean ± S E M)*

	Basal	Isoprenaline	Basal	Nicotinic acid	Nicotinic acid + isoprenaline
Cyclic AMP (nmol/l)	17 4±4 9	41 0±8 3	18 7±6 4	13 9±3 7	37 8±7 4
FFA (mmol/l)	0 66±0 06	1 61±0 24	0 79±0 11	0 49±0 04	0 46±0 05

nicotinic acid alone resulted in no significant change in FFA or cyclic AMP concentrations compared with basal values When isoprenaline was infused in combination with nicotinic acid cyclic AMP concentrations were significantly increased above basal concentrations ($p<0\ 002$) and were not different from values obtained with isoprenaline alone FFA concentrations were significantly reduced ($p<0\ 002$) however during the combined infusion of isoprenaline and nicotinic acid compared with isoprenaline alone

DISCUSSION

In the patients with AMI described here elevated plasma FFA and catecholamines were not associated with high plasma concentrations of cyclic AMP In experimental situations substantial amounts of ^{3}H nicotinic acid accumulate in adipose tissue (3) suggesting that the in vivo FFA lowering effects of this agent are achieved by a reduction in intracellular cyclic AMP concentrations as described in isolated fat cell studies (2) However inhibition of lipolysis with the NAA in these patients did not result in a fall in plasma nucleotide concentrations In more severely ill patients with AMI and marked elevation of plasma catecholamines plasma cyclic AMP can be elevated (12 14) In order to reproduce this situation plasma cyclic AMP concentrations were increased above the reference range by the i v administration of isoprenaline to anaesthetized dogs In agreement with the human studies however inhibition of lipolysis did not affect isoprenaline stimulated nucleotide concentrations

The reason for the higher plasma cyclic AMP concentrations in the patients who received NAA compared with placebo treated patients after 20 and 24 hours of treatment is not clear since our results show no change in plasma catecholamine concentrations Experimental reduction of plasma FFA concentrations however increases the secretion rate of glucagon (7) this might result in elevation of plasma cyclic AMP

These results suggest that adipose tissue does not release significant amounts of nucleotide into plasma even when lipolysis is increased and can therefore be discounted as an important source of extracellular cyclic AMP in man

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Immunofluorescent Demonstration of the Presence of Protein HC on the Surface of Human Lymphocytes

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ABSTRACT. Indirect immunofluorescence was used to demonstrate the presence of protein HC on the surface of a large percentage of normal human peripheral blood lymphocytes. Protein HC is a recently described charge heterogeneous, complex forming glycoprotein normally present in human plasma, urine and cerebrospinal fluid. The synthesis of protein HC by lymphocytes was indicated by the removal of the glycoprotein from the cell surfaces on trypsinization of the cells followed by the reappearance of the protein on continued cultivation of the cells.

A low molecular weight glycoprotein has recently been isolated from normal human urine and its presence in normal human plasma in a concentration of about 100 mg/l has been established (5). The glycoprotein was tentatively called protein HC (Human Complex forming glycoprotein Heterogeneous in Charge) because of its marked charge heterogeneity and its normal occurrence as complexes with other plasma proteins. The quantitatively dominating complex was an IgA–protein HC complex. The present work demonstrates the occurrence of protein HC on the surfaces of a large percentage of normal human peripheral blood lymphocytes and indicates the synthesis of the glycoprotein by these cells.

MATERIAL

Human protein HC and monospecific rabbit antiserum against protein HC were prepared as described earlier (5). Human albumin, polyclonal IgG and β_2-microglobulin were available at the laboratory. Fluorescein isothiocyanate (FITC)-conjugated sheep antibodies against rabbit IgG was purchased from Statens Bakteriologiska Laboratorium, Stockholm. The mean fluorescein protein molar ratio of the conjugates was 4.1.

Hanks' balanced salt solution (HBSS) and modified medium 199 were supplied from Flow Laboratories. Ficoll 400 from Pharmacia and sodium metrizoate 32.8% (w/v) from Nyegaard & Co., Oslo, Norway. Trypsin (E.C. 3.4.21.4) was obtained from Difco. All other chemicals were of reagent grade.

METHODS

Isolation of lymphocytes. Heparinized venous blood was obtained from five healthy volunteers (4 males, 1 female). Lymphocytes were isolated as described by Mellstedt & Holm (3) by sedimentation through gelatine, followed by removal of phagocytic cells after ingestion of iron powder and centrifugation through a Ficoll–metrizoate gradient.

Trypsinization of lymphocytes. The procedure of Mellstedt et al. (2) was used.

Inhibition experiments. The antibody titer of the rabbit antiprotein HC antiserum was determined according to Becker (1). Purified protein HC was added to aliquots of the antiserum in amounts corresponding to 1.5, 3 and 9 times the antibody titer. Purified IgG, β_2-microglobulin and albumin in molar amounts equivalent to the various protein HC additions were also added to separate aliquots of the antiserum. After incubation for one hour at 37°C followed by incubation over night at 4°C the absorbed antiserum aliquots were cleared by centrifugation.

Indirect immunofluorescence. The isolated lymphocytes were washed twice in cold HBSS containing 0.15 M Tris-HCl buffer, pH 7.4, and 2×10^6 cells were then incubated with 50 μl rabbit antiserum or serum from non-immunized rabbits for 30 min at 4°C. Thereafter the cells were washed twice as described above, incubated for 30 min at 4°C with 50 μl of a solution of FITC-conjugated sheep antibodies against rabbit IgG diluted 1:5 with phosphate buffered saline (PBS), pH 7.8, washed twice and mounted with phosphate buffered glycerol, pH 7.8. Readings were made on a Leitz Orthoplan fluorescence microscope with a Ploem epiilluminator equipped with the following filters: GG 475, KP 490 (two), TK 510 and K 515. Each microscopic field was first examined in phase contrast to identify lymphocytes and then in epiillumination to identify cells with membrane fluorescence. 100–200 cells were counted in each preparation and the

Table I. *Percentages of isolated lymphocytes showing membrane fluorescence*

Incubation medium prior to incubation in FITC conjugated sheep antibodies against rabbit IgG	Subject no.				
	1 (♂ 33 y.)	2 (♂ 28 y.)	3 (♀ 29 y.)	4 (♂ 26 y.)	5 (♂ 29 y.)
Rabbit antiprotein HC antiserum	86	73	85	86	79
Normal rabbit serum	6	2	5	5	6
PBS	0–1	0–1	0–1	0–1	0–1
Rabbit antiprotein HC antiserum absorbed with					
Purified protein HC	13	8	N.D.	N.D.	N.D.
β microglobulin, IgG or albumin	80–90	70–80	N.D.	N.D.	N.D.

N.D. = not done.

percentages of cells showing fluorescence were calculated.

RESULTS

After the purification procedure the cell suspensions contained 92–97% lymphocytes as judged from Pappenheim stained smears.

When various lymphocyte preparations from five individuals were incubated first with rabbit antiprotein HC antiserum and then with FITC conjugated sheep antibodies against rabbit IgG, 73–86% of the cells showed patchy or segmental membrane fluorescence (Table I). No fluorescent cells were observed when the lymphocyte preparations were incubated with PBS instead of rabbit antiserum. When the rabbit antiserum was replaced by serum from non-immunized rabbits, 1.5–6% of the cells showed fluorescence. Absorption of the rabbit antiserum with purified protein HC in amounts equivalent to 1.5, 3 or 9 times the antiserum titer drastically decreased the percentages of cells showing fluorescence (Table I), whereas absorption of the antiserum with equivalent molar amounts of IgG, β microglobulin or albumin did not diminish the number of fluorescent cells.

When the isolated lymphocytes from one volunteer (no. 5) were subjected to trypsinization, washed and thereafter immediately incubated with antiprotein HC antiserum, only 9% of the cells showed membrane fluorescence with a fluorescence intensity equal to that of non-trypsinized cells. Of the remaining cells some were completely negative but most had retained a few weakly fluorescent spots on their membranes. After prolonged incubation over night in tissue culture medium without trypsin, 36% of the cells showed clear membrane fluorescence when incubated with antiprotein HC antiserum.

DISCUSSION

73–86% of the cells of purified lymphocyte populations from five healthy individuals showed strong membrane fluorescence when incubated with rabbit antiserum against protein HC followed by incubation with FITC conjugated sheep antibodies against rabbit IgG. Absorption of the rabbit antiserum with large amounts of human β microglobulin, IgG or albumin did not diminish the number of fluorescent cells. But absorption of the antiserum with pure protein HC in an amount equal to 1.5 times its antibody titer virtually abolished all fluorescence. We therefore conclude that a large percentage of normal human lymphocytes carry on their cell membranes an antigenic material identical with or sharing antigenic determinants with protein HC.

The finding of 2–6% of cells showing membrane fluorescence when normal rabbit serum was used for incubation instead of antiprotein HC antiserum is probably due to contamination of the lymphocyte populations with a small number of monocytes which have receptors for rabbit IgG (4) and may be virtually impossible to differentiate from lymphocytes on phase contrast microscopy.

The presence of the protein HC related material on the cell surfaces of lymphocytes means that the material is either produced by these cells or absorbed from plasma. Although the experiments performed cannot rule out the latter possibility, the trypsinization experiments and the careful washing procedure support the former hypothesis.

It should be pointed out that not all but merely 73–86% of the cells of the lymphocyte populations show the presence of the protein HC related material on their cell surfaces in this investigation. This raises the questions whether the presence or absence of the protein HC related material on the

cell surfaces of lymphocytes define two subpopulations of lymphocytes and if this is the case how these subpopulations are related to the B and T cell populations

Although the biological function of protein HC is unknown the present knowledge of its charge heterogeneity and of its presence on the surfaces of lymphocytes prompts to investigations concerning the relation between this glycoprotein and other heterogeneous glycoproteins like the immunoglobulins and the HLA antigens which are present on the cell surfaces of some or all nucleated cells

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Systemic Lupus Erythematosus in Twin Sisters Following Ten Years of Hyperglobulinemic Purpura (Waldenstrom)

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ABSTRACT Uniovular twin sisters have been diagnosed 10 years ago as having hyperglobulinemic purpura (Waldenström) at age 12 The diagnosis was documented by purpura of the lower extremities, increased γ globulin after serum electrophoresis, and increased 7S component upon ultracentrifugation In addition there was an elevated ESR, a positive rheumatoid arthritis latex test, and their LE prep was negative at that time At a later date, however, both of them developed polyarthritis After 9 years for the one and 10 years for the other, their LE prep became strongly and constantly positive, while their γ globulin remained within abnormal limits

A review of the literature revealed about 20 cases which were considered to be primary hyperglobulinemic purpura (Waldenstrom) (3) Generally this disease mainly of females is characterized by recurrent purpura of lower extremities precipitated by wearing tight garments or standing and often followed by residual hyperpigmentation (3) Abnormal laboratory findings include an increase in ESR increase in γ globulin polyclones increase in 7S component a positive rheumatoid arthritis (RA) test and often an abnormal Rumpell Leed s Tourniquet test (3) A follow up period of at least 2 years is necessary to exclude other underlying disease (3) It has been suggested that heredity might play a role in the development of hypergammaglobulinemia and systemic lupus erythematosus (SLE) (14) In support of that hypothesis SLE was reported by Leonhardt in 1957 in 3 of 14 siblings (14) Four of his patients had greatly increased γ globulins and the other six had values above the normal range

Other arguments favoring a hereditary predisposition for SLE are Davis and Gutrige reported SLE in uniovular twins (6) Agranat et al SLE in two sisters (1) Vegenhals and Burgerson s demonstration of SLE in twin sisters (20) the documentation of the familial occurrence of SLE by Griffin et al (9) in a father and his daughter and the seeming familial occurrence of SLE and RA reported by others (2 5 7 10)

METHODS MATERIAL AND CASE PRESENTATION

Case I

A 12 year-old white female was seen at Wadley Research Institutes for the first time in 1964 because of purpuric lesions on her lower legs These lesions had appeared intermittently for several months and were aggravated by standing and exercise They had not been painful or itching but had left small brown freckle like spots Concomitant with the appearance of the lesions the patient had a low-grade fever bilateral parotid swelling and slightly enlarged spleen The remainder of the physical examination was within normal limits and the patient was active with no other complaints such as joint pain nausea vomiting or allergy

The laboratory findings during the first 4 years revealed constant leukopenia increase in ESR and γ-globulin on protein electrophoresis (Fig 1) as well as a 7S component on ultracentrifugation LE prep performed in 1964 was negative and RA latex test positive Other tests demonstrated a negative heterophil titer and a normal coagulation work up urinalysis was normal Immunoelect phoresis done in 1964 against antihuma

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Right Atrial Monophasic Action Potential in Healthy Males

Studies during Spontaneous Sinus Rhythm and Atrial Pacing

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ABSTRACT Right atrial monophasic action potentials (MAP) have been recorded in 40 healthy males At least one MAP recording was performed in each individual during spontaneous sinus rhythm Right atrial pacing and simultaneous MAP recording were performed in 25 of the 40 individuals The paced cycle length was successively decreased in steps of 100 msec between 800 and 400 msec The durations of the MAP at 50 and 90% repolarization and the relative repolarization rate during phase 3 (RRR ph 3) were calculated and normal values for the variables are given A correlation was demonstrated between the duration of the MAP and the cycle length—the longer the cycle length the longer the duration of the MAP—both during sinus rhythm and during atrial pacing A significant correlation was also shown between the RRR ph 3 and the duration of the MAP at 90% repolarization—the shorter the MAP, the faster the RRR ph 3 One age group (45–54 years) deviated significantly from the rest in some respects, but in general there was no age trend in the whole material

Our interest in recording monophasic action potentials (MAP) was aroused in 1966 when Korsgren et al (21) reported a method of obtaining MAP from the right atrium of the intact human heart using the transvenous route In 1971 Olsson et al described a modified suction electrode catheter (24) and since then this catheter has been further developed The suction electrode technique has been used in the investigation of patients with different kinds of atrial arrhythmias Short MAP duration or a slow phase for depolarization (22 23) was demonstrated in a few cases These findings might indicate the mechanism of the arrhythmias in these patients The different findings are however difficult to evaluate due to lack of normal values in healthy individuals

The aim of this study is therefore to describe MAPs in healthy male volunteers in spontaneous sinus rhythm and during atrial pacing with special reference to alterations due to changes in the heart rate (HR)

MATERIAL

The material consisted of 40 healthy male volunteers The clinical history physical examination ECG and chest X ray were normal in every case All individuals studied had received adequate information about the procedure including risks before agreeing to participate

In nine of 49 volunteers to be investigated we were not able to obtain satisfactory MAP recordings for technical reasons which will be discussed later The final material thus consisted of 40 individuals divided into four age groups of ten individuals each The age limits for each group were group 1 25–34 years (mean 30) group 2 35–44 (mean 40) group 3 45–54 (mean 49) and group 4 55–64 years (mean 58)

METHODS

The volunteers were investigated in the post absorptive state None of them had received any premedication before the investigation which was performed in the supine position

A venous blood sample was taken at the beginning of the investigation for analyses of serum levels of sodium potassium calcium chlorides phosphate bicarbonate thyroxin and triiodothyronine All these values were normal

The MAP recordings were performed with the suction electrode technique as described by Olsson et al (24) The modified MAP catheter used (Fig 1) consisted of a special 3 lumen catheter made of green Ödman Ledin radio opaque polythene catheter material (ABO Trading Kulla

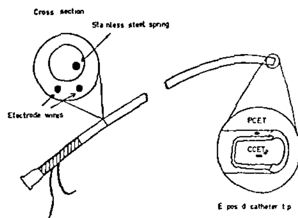


Fig 1 Schematic representation of the MAP catheter

vik Sweden) The total catheter length was 100 cm o d 2 8 mm i d 1 5 mm The copper electrode material was embedded in the catheter wall The central catheter electrode terminal (CCET) ended in the lumen 1–3 mm from the tip and the peripheral catheter electrode terminal (PCET) on the outside of the catheter at a distance of 3–4 mm from the tip The lumen of the catheter contained a reinforcing stainless steel spring in order to make the catheter sufficiently stiff to be manipulated into a perpendicular position against the right atrial wall

The MAP catheter was inserted percutaneously into the right femoral vein and advanced to the right atrium under fluoroscopic control As the catheter was rather stiff care was taken to avoid forming loops inside the veins to avoid damage to the vessels If there was difficulty in passing the pelvic or hepatic veins a soft thin stainless steel guide wire was inserted via the lumen of the MAP catheter and advanced 5–10 cm beyond the tip With this technique the right atrium could be reached in all but four of the 49 volunteers

In the right atrium the catheter was gently pressed against the wall in order to get a stable perpendicular position If a monophasic deviation appeared suction was applied (−350 mmHg) for not more than 2 min

The electrodes were connected to the amplifier unit with sterile cables A 3 way stop-cock allowed either infusion of saline or application of suction through the MAP catheter The suction was applied via a capacitance bottle (24)

The MAP signal together with a bipolar right atrial electrogram (RAE) (between PCET and left leg) and a precordial ECG was presented on a display oscilloscope (Airmec type 279) an Ultralette writer 567 and an FM tape recorder (Honeywell 5600) The paper speed was 100 mm/sec

The MAP signal (CCET PCET) was amplified with a DC-coupled differential amplifier and a preamplifier with an input impedance of 100 000 Mohm The equipment allowed proper reproduction between DC and 1 000 Hz on the Ultralette writer and from DC to 625 Hz on the tape recorder This clearly included all parts of the MAP signal The catheter electrode tissue impedance has been previously tested between 1 and 1 000 Hz with and without suction against a fresh non beating piece of human heart tissue in 37°C saline solution The maximal impedance was 55 kohm recorded at 5 Hz and decreased to 10 kohm at 200–1 000 Hz The very high input impedance minimized distortion of the signals A serial input impedance of 680 kohm provided electrical security for the individuals against leakage currents from the amplifier

The Ethical Committee of the Medical Faculty reviewed the procedure and accepted the design of the study

Spontaneous sinus rhythm

The intention in designing this study was to get at least three recordings during spontaneous sinus rhythm from each of the 40 individuals In two of the nine excluded cases the investigation was interrupted due to electrical failure of the MAP catheter In another four cases the pelvic veins could not be passed One individual developed atrial fibrillation in connection with manipulation of the MAP catheter and no recordings were made during sinus rhythm The last two cases were discarded because of injury potentials in the RA electrogram

The recordings were meant to be taken from the low middle and high parts of the atrium In only one case was it possible to place the MAP catheter in an optimal way low in the atrium In most cases it was easy to get a middle recording In several cases no high registration could be performed because of difficulties in manipulating the catheter high in the atrium

The MAP was discarded if the RA electrogram showed P Ta elevation (Fig 2) or if the recordings had irregularities making them difficult to calculate In some of the determinations the curves had to be discarded because of difficulties in determining the baseline In all of the 40 accepted cases at least one MAP recording was performed during spontaneous sinus rhythm

Atrial pacing

The aim of the investigation also included MAP recording during pacemaker induced variations in HR Thus atrial pacing was attempted in all cases

The pacemaker catheter used for the pacing investigation was mostly inserted via a left cubital vein and as a rule placed high in the right atrium near the sinus node The catheter was connected to a specially constructed pacemaker (Elema Schonander AB Sweden) This produced square wave impulses of 2 msec duration and of constant current The basic cycle length had a precision of ±1 msec

In 14 cases it was not possible to perform atrial pacing and simultaneously get an acceptable MAP signal In one case pacing was not performed as the individual developed atrial fibrillation in connection with the manipulation of the MAP catheter Altogether 25 pacing investigations were performed in which at least the MAP signal in two of the frequencies used could be calculated

The basic pacing cycle lengths used were 800 700 600 500 and 400 msec MAP recordings were performed during atrial pacing The duration of the recordings was about 30 sec for each pacing frequency Only the last five beats at each pacing frequency were calculated to avoid any effect of earlier frequencies on the duration of the MAP (20)

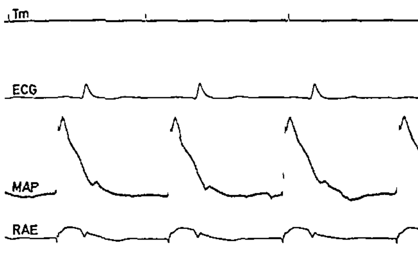


Fig 2 Example of right atrial MAP excluded due to P–Ta elevation in the right atrial electrogram (*RAE*)

The complete atrial pacings with acceptable MAP signals are shown in Table II Several of the recordings of some of the designated cycle lengths had to be discarded for various reasons In four cases it was not possible to pace at a cycle length of 800 msec because of interference from the spontaneous HR and the same reason was the cause of failure in two individuals at a paced cycle length of 700 msec Difficulties in determining the baseline and drifting of the baseline made it impossible to calculate the MAP signal in 10 investigations at a paced cycle length of 500 msec and in 14 at 400 msec (Fig 3)

Analysis

The analysis of a single MAP is illustrated in Fig 4 The amplitude of the MAP (*A*) was expressed in mV In only three cases was the transition between phases 1–2 and 3 distinguishable The duration of these phases has therefore not been calculated The duration was measured at 50% (*c*) and 90% (*d*) repolarization and expressed in msec The duration of the MAP at 50% repolarization includes phases 1+2 and to a lesser extent phases 0 and 3 and might be used as an approximation of the duration of phases 1+2 (26) Duration of phase 0 (*b*) was defined as the time between 10% (*B*) and 90% (*A–D*) depolarization (msec) In these recordings where the slope of depolarization was not stable and no rapid upstroke could be calculated the duration phase 0 (*b*) was regarded as the time between 10% depolarization and the visible part of the MAP recording at 90% depolarization RRR ph 3 was calculated from the difference in time between 50% and 90% repolarization (*e*) The value was transformed into %/sec (22) according to the formula RRR ph 3=40×1000/*e* The interval from the beginning of the P wave in the RAE to the onset of phase 0 of the MAP was expressed in msec (*a*) The preceding cycle length was measured from the onset of phase 0 of the preceding MAP to the same point of the actual MAP and expressed in msec All individual values are means of five consecutive beats In no case did individual consecutive values differ more than 10% from their mean

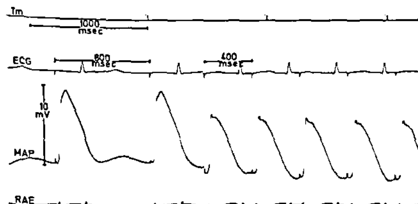


Fig 3 Example of MAP recording at a paced cycle length of 400 msec impossible to calculate because of difficulties in defining the base line

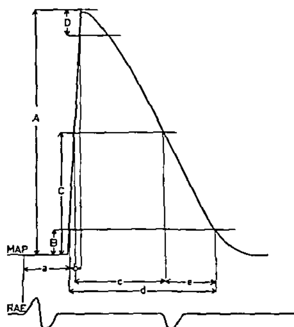


Fig 4 Analyses of a single right atrial MAP

RESULTS

Spontaneous Sinus Rhythm

Age dependence

An example of a recording is given in Fig 3 (left) The results of the analyses of right atrial MAP during spontaneous sinus rhythm in the four age groups of 10 individuals each are shown in Table I The umber of recordings differed between individuals In the analysis of variance only the first MAP recordings have been used

The length of the sinus cycle differs somewhat but not significantly between the various group means Neither are there any significant differences between the groups with regard to P phase 0 the duration of phase 0 or the amplitude of the MAP

Durations of the MAP at 50% and 90% repolarization and RRR ph 3 together with *F* values of the analysis of variance are given in Fig 5 There are significant differences between age group 3 and the other groups at 90% repolarization For reasons mentioned in the discussion this difference has been neglected and the four groups are regarded as an entity in further calculations

MAP amplitude

The amplitude of the MAP during spontaneous sinus rhythm ranges between 2 0 and 13 4 mV (mean 6 2 S D 2 6)

P phase 0

The interval from the onset of P wave of the RAE to phase 0 ranges between 5 and 40 msec (mean 19 S D 9)

Duration of phases 0–3

The duration of phase 0 of the MAP ranges between 2 and 57 msec (mean 24 S D 16) In the majority of the recordings it has not been possible either to differentiate between phases 1 and 2 of the MAP or to decide the transition between phases 2 and 3 These variables have therefore not been considered in the final analysis

MAP duration

The duration of the MAP at 50% repolarization ranges between 102 and 225 msec (mean 160 S D 26 6) and at 90% repolarization between 197 and 350 msec (mean 271 S D 38 5) (Table I)

RRR phase 3

The values of the RRR ph 3 are shown in Table I The range is 260–909%/sec (mean 425 S D 135)

MAP duration—cycle length in sinus rhythm

The relation between the duration of the MAP at 90% repolarization (Y) and the cycle length (X) during spontaneous sinus rhythm is depicted in Fig 6 for the total investigation The regression is $Y=188\ 8+0\ 0962X$ ($r=0\ 32$ $t_r=2\ 96$ $s_{y.x}=35\ 2$) The

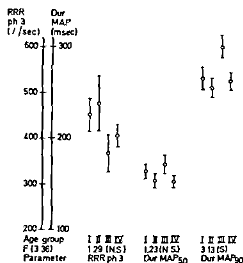


Fig 5 Duration of MAP at 50% (MAP_{50}) and 90% (MAP_{90}) repolarization and RRR ph 3 in the four age groups (mean±S E M)

Table I *Results of analyses of right atrial MAP during sinus rhythm in the four age groups*

L=low M=middle H=high position of the MAP catheter

Subj no	Cycle length (msec)	Fluoro-scopic position	P ph 0 (msec)	Ampl MAP (mV)	ph 0 (msec)	MAP duration (msec)		RRR ph 3 (%/sec)
						50% repol	90% repol	
Age group 1								
1	659	M	20	4 7	2	150	233	494
	748	H	10	3 4	65	105	225	500
3	1 007	M	5	9 8	40	102	197	533
	1 060	M	5	5 7	32	125	203	588
	1 040	M	40	5 2	32	148	212	645
4	820	H	15	6 3	40	167	241	625
	779	H	25	2 9	–	167	241	555
	796	M	25	6 9	40	147	258	440
6	1 063	H	20	6 7	45	165	323	270
0	880	M	20	2 5	15	177	302	3[illegible]8
	895	M	20	4 2	20	178	300	342
22	840	H	20	8 9	7	178	288	367
	951	M	22	5 6	42	173	269	449
24	776	M	16	8 9	10	173	252	563
	866	H	36	4 9	12	195	273	5[illegible]6
25	936	M	15	13 4	20	178	294	377
	896	H	40	2 8	21	145	267	348
26	877	–	30	8 5	40	150	235	533
38	748	H	5	4 9	5	198	29[illegible]	471
	798	M	20	7 0	10	135	235	408
Age group 2								
2	1 038	M	10	4 4	5	170	216	909
5	709	H	15	7 8	50	142	233	494
7	782	H	–	4 6	15	115	270	270
9	830	M	11	6 3	12	165	240	597
17	816	M	15	7 4	30	131	239	377
	879	H	12	9 7	40	172	283	367
18	890	H	20	2 2	25	162	272	370
	950	M	25	6 4	30	166	263	421
19	598	M	5	7 0	22	154	279	348
37	845	H	15	3 8	43	182	316	323
	918	H	16	12 6	20	155	280	333
39	669	M	15	10 0	57	127	213	606
	670	M	25	6 3	50	180	243	755
42	1 070	H	17	2 9	12	188	282	460
	1 069	H	18	6 0	13	198	304	408
Age group 3								
12	1 080	M	30	2 9	29	198	307	388
	995	M	18	8 3	22	175	270	471
14	783	H	30	7 7	12	181	269	506
	810	M	20	7 8	16	170	263	471
21	862	H	5	8 4	12	225	350	348
	855	H	15	5 6	15	230	370	305
28	1 086	M	17	7 9	45	205	337	333
	1 103	H	12	7 1	55	181	306	342
	1 093	M	4	7 8	56	196	333	320
30	919	H	30	3 4	11	172	324	296
	880	H	17	8 1	20	152	333	245
	908	H	20	5 3	20	137	318	234
31	892	M	26	4 3	8	151	307	261
	944	M	24	4 6	10	162	299	315
32	682	M	15	7 2	48	177	300	348
	671	M	17	8 9	32	188	320	308
33	874	M	30	4 1	5	157	313	260
34	732	H	30	11 0	52	125	207	666
	722	H	35	4 5	4	145	239	430
	754	H	25	8 6	45	126	255	351
41	952	M	8	5 1	25	128	292	274
	988	H	30	4 5	13	161	301	305

Table I (*Cont*)

Subj no	Cycle length (msec)	Fluoroscopic position	P ph 0 (msec)	Ampl MAP (mV)	ph 0 (msec)	MAP duration (msec) 50% repol	MAP duration (msec) 90% repol	RRR ph 3 (%/sec)
Age group 4								
11	675	M	5	8 5	20	173	295	351
	680	H	35	6 0	5	182	286	396
	690	M	7	10 2	15	162	260	421
29	695	M	22	3 3	9	156	238	526
	810	M	18	6 7	17	138	236	444
	850	M	28	5 6	8	130	222	455
35	806	M	40	4 4	3	166	282	351
	761	M	35	2 9	2	169	286	345
	805	M	30	3 3	2	172	259	471
40	653	H	25	7 4	17	111	199	455
	669	M	2	3 3	13	141	221	556
43	965	H	28	4 4	19	141	291	292
	930	M	20	4 7	13	182	291	392
44	915	M	13	2 0	19	180	263	488
	800	H	25	2 9	18	144	228	541
46	834	L	21	6 6	55	125	253	381
	728	M	40	10 3	40	115	237	348
47	864	M	13	5 4	17	161	251	494
	790	M	10	7 2	10	160	260	417
48	885	M	21	6 5	19	150	274	357
	844	H	20	12 9	15	165	269	396
49	868	H	35	8 1	20	160	280	364
	823	M	22	5 1	14	186	285	444

correlation is weak mainly because of the inter and intraindividual variations In order to eliminate the latter only the first recording in each individual has been used which gives $Y=178\ 9+0\ 1091X$ ($r=0\ 37$ $t_r=2\ 45$ $s_{yx}=36\ 7$)

The relation between the duration of MAP at 50% repolarization and the cycle length is likewise weak but still significant when the total amount of recordings are used (Fig 7) The regression is $Y=115\ 5+0\ 0531X$ ($r=0\ 25$ $t_r=2\ 32$ $s_{yx}=25\ 1$) The first recordings yield $Y=110\ 9+0\ 0584X$ ($r=0\ 28$ $t=1\ 79$ $s_{yx}=25\ 8$)

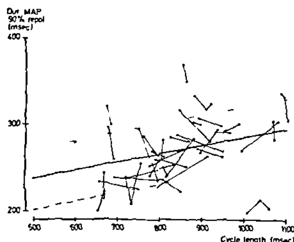


Fig 6 Duration of MAP at 90% repolarization and cycle length during spontaneous sinus rhythm (all recordings) Regression line $\pm 2\ s_{yx}$ is indicated Multiple recordings within the same atrium are connected with thin lines

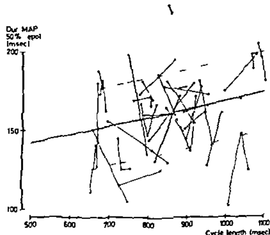


Fig 7 Relation between the duration of MAP at 50% repolarization and cycle length during spontaneous sinus rhythm All recordings are represented Recordings within the same atrium are connected with thin lines The regression line $\pm 2\ s_{yx}$ is indicated

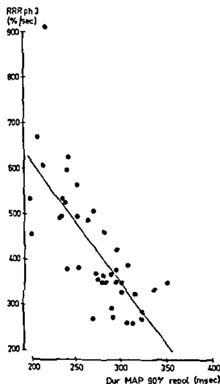


Fig 8 Relation between the RRR ph 3 and the duration of MAP at 90% repolarization during spontaneous sinus rhythm The regression line is indicated The first recording of each individual is used

The correlation between the RRR ph 3 and the cycle length is not significant either when the first or the total amount of recordings are used

MAP duration—RRR ph 3

The relation between the duration of the MAP at 90% repolarization and RRR ph 3 is depicted in Fig 8 The correlation is good and the regression is $Y-1147\ 8-2\ 6739X$ ($r=0\ 75$ $t_r=6\ 92$ $s_{yx}=92\ 96$) The correlation between the duration of the MAP at 50% repolarization and the RRR ph 3 is not significant

Adjustment with regard to cycle length

In order to eliminate the influence of cycle length on the duration of the MAP the values at 90% repolarization have been transformed to correspond to a cycle length of 800 msec according to the formula above $Y=178\ 9+0\ 1091X$ The transformed duration of the MAP at 90% repolarization is 266 msec (S D 38 5 S E 6 1) At 50% repolarization the duration is 157 msec (S D 26 6 S E 4 2) transformed according to the formula above $Y=110\ 9+0\ 0584X$

Atrial Pacing

It was possible to perform atrial pacing and simultaneously record the MAP in two successive cycle lengths in 25 of 40 individuals The intention was to follow the MAP variables during paced cycle lengths of 800 700 600 500 and 400 msec This was achieved in only nine investigations (Table II)

Age dependence

The duration of the MAP at 90% repolarization is shown in Table II Different numbers of recordings have been performed in the different age groups at the five cycle lengths used There are no significant differences between the mean values of the age groups at any paced frequency

The corresponding values for the duration of the MAP at 50% repolarization are shown in Table III There is a significant difference between age group 3 and the other groups at a paced cycle length of 800 msec This difference has been accepted for the reasons mentioned previously in group 3 during sinus rhythm

The RRR ph 3 in the different age groups at the various cycle lengths is shown in Table IV No significant differences were found between the four groups

MAP duration—paced cycle length

The duration of the MAP at 90% repolarization at different paced cycle lengths is shown in Table V There is a significant decrease in the duration with decreasing cycle length in all the steps (Fig 9) There are strong individual correlations between these variables The correlation coefficients are between 0 87 and 1 00 (except case 44 −0 70) in the recordings including 3–5 cycle lengths The individuals differ greatly however both in the slope of the regression line and in the initial values (Fig 9) The individual regression coefficients between the individuals vary from 2 5 to 22 Because of this the correlation between the duration of the MAP and the cycle length is not significant for the total material ($r=0\ 10$)

A similar relation exists between the duration of the MAP at 50% repolarization and the paced cycle length (Fig 10 Table V)

RRR ph 3 shows a significant increase between

Table II *Duration of the MAP at 90% repolarization (msec) during atrial pacing with different paced cycle lengths*

The *F* values in the analysis of variance are given below The statistical variables of the total amount of recordings in each cycle length are given at the foot of the Table (n s = not significant)

Age group	Subj no	Paced cycle length (msec) 800	700	600	500	400
1	3	185	168	166	–	–
	20	249	242	–	–	–
	22	260	250	242	241	–
	24	248	242	241	240	228
	25	293	279	271	–	–
	26	238	220	–	–	–
	38	242	231	231	225	215
2	2	215	206	204	–	–
	9	–	226	213	–	–
	17	280	251	232	223	–
	18	269	234	234	–	–
	19	–	–	294	282	250
	37	283	263	237	237	220
	42	280	270	270	260	254
3	12	276	266	260	260	252
	14	232	226	220	214	–
	21	379	367	359	348	328
	28	261	262	233	221	–
	30	325	307	304	293	280
	41	253	248	230	–	–
4	11	–	–	255	250	250
	35	257	256	253	244	243
	43	276	245	239	–	–
	44	236	230	229	229	230
	46	–	235	224	–	–
		F = 1 38 (n s)	2 11 (n s)	1 04 (n s)	0 58 (n s)	3 85 (n s)
1+2+3+4	Mean	264	249	245	251	250
	S D	39 5	37 5	38 0	34 8	31 7
	S E	8 6	7 8	7 9	9 0	9 6
	n	21	23	23	15	11



Fig 9 Relation between the duration of MAP at 90% repolarization and paced cycle lengths in the atrial pacing study A thick line indicates the mean increase in duration between the different cycle length steps

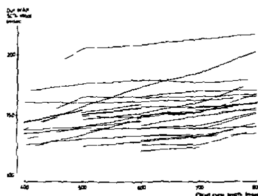


Fig 10 Relation between the duration of MAP at 50% repolarization and the paced cycle length The thick lines indicate the mean increase in MAP duration between the different paced cycle lengths

Table III *Duration of the MAP at 50% repolarization (msec) during atrial pacing of different cycle lengths*
The statistical variables correspond to Table II (s=significant n s =not significant)

Age group	Subj no	Paced cycle length (msec) 800	700	600	500	400
1	3	138	126	126	–	–
	20	152	139	–	–	–
	22	160	158	149	150	–
	24	158	155	150	141	138
	25	168	166	165		–
	26	156	150	–	–	–
	38	139	133	134	131	123
2	2	153	142	140	–	–
	9	–	150	142	–	–
	17	144	132	129	125	–
	18	160	157	158	–	–
	19	–	–	160	153	142
	37	141	140	140	140	135
	42	155	153	149	134	123
3	12	180	178	180	177	170
	14	178	161	152	147	–
	21	218	214	209	206	177
	28	168	153	147	136	–
	30	204	186	174	158	138
	41	135	133	130	–	–
4	11	–	–	146	141	130
	35	171	171	166	166	144
	43	141	134	134	–	–
	44	166	163	162	161	161
	46	–	124	121	–	–
		F=3 34 (s)	2 87 (n s)	1 55 (n s)	1 86 (n s)	2 37 (n s)
1+2+3+4	Mean	161	153	151	151	144
	S D	21 2	21 1	20 0	20 7	18 1
	S E	4 6	4 4	4 2	5 3	5 5
	n	21	23	23	15	11

700 and 600 msec but the remaining paced cycle length steps show no significant differences

Errors of the Method

The statistical analysis of differences between the means of the age groups have been examined by one way analysis of variance using the F ratio (F) as test variable The relations between the paced cycle length and the MAP variables have been based upon paired individual differences of these variables giving dependent t tests (t_{dep}) of means of successive cycle length groups This method was used as it was not possible to get MAP recordings at all paced cycle lengths

The relation between the cycle length (X) and the MAP variables (Y) during spontaneous sinus rhythm was analysed by linear regression using the formula $Y=a+bx$ The correlation coefficients (r) were tested by t test (t) The residual standard deviations of Y (s_{yx}) were also calculated

Ten consecutive beats of ten different recordings were tested for randomness with the mean square successive difference test No systematic changes were revealed in the duration of the MAP or RRR ph 3 The cycle length during sinus rhythm however varied consistently Some recordings showed a decreasing some an increasing trend and in one recording there was a cyclic variation This fact is of minor importance as the variations—though significant—were small and in our calculations the mean of five consecutive beats was used

The variation due to the analysis of a single MAP was estimated from the results of analysis of double determinations of two photocopied recordings in 15 individuals The error of a single determination was calculated as $s=\sqrt{\Sigma d_i^2/2n}$ (d_i=difference between

Table IV *Relative repolarization rate during phase 3 of the MAP (%/sec) during atrial pacing at different cycle lengths*

Age group	Subj no	Paced cycle length (msec)				
		800	700	600	500	400
1	3	889	1 000	1 053	–	–
	20	421	396	–	–	–
	22	430	471	465	482	–
	24	488	506	482	449	488
	25	354	396	426	–	–
	26	541	645	–	–	–
	38	392	412	417	430	440
2	2	741	714	714	–	–
	9	–	588	635	–	–
	17	331	385	412	417	–
	18	426	580	606	–	–
	19	–	–	305	320	381
	37	303	325	421	421	482
	42	339	364	351	336	323
3	12	476	526	571	548	556
	14	769	635	606	615	–
	21	260	274	280	296	290
	28	460	377	513	526	–
	30	339	342	317	301	292
	41	342	360	421	–	–
4	11	–	–	377	377	342
	35	471	476	465	519	412
	43	301	367	388	–	–
	44	645	678	678	667	656
	46	–	440	449	–	–
		$F=$ 0 20 (n s)	0 59 (n s)	0 44 (n s)	1 00 (n s)	0 36 (n s)
1+2+3+4	Mean	463	489	494	446	424
	S D	168 7	165 7	170 0	113 0	115 4
	S E	36 8	34 6	35 5	29 2	34 8
	n	21	23	23	15	11

2 analyses n=number of pairs) This error is small and besides individual values are means of measurements of five successive beats (Table VI I)

In order to exclude systematic differences in the durations and RRR ph 3 of the MAP with regard to the recording sites high positions of the MAP catheter were compared to middle positions using the t test of paired differences The comparison covered the 17 individuals in whom a high as well as a middle recording was performed No systematic differences were found Using the same method the recordings with the shortest and longest P phase 0 intervals were tested for systematic differences No differences were revealed in the 31 individuals (Table I) in whom the comparison was possible

In four individuals MAP recordings were performed twice at identical positions and also at a different position The errors of these recordings were calculated as $s=\sqrt{\Sigma d_i^2/2n}$ (d_i=difference between 2 positions (identical or different) n=number of pairs)

From Table VI (II*a* *b*) it is evident that the variation in the duration of the MAP at 90% repolarization is very small for recordings at identical sites compared to different positions A similar tendency exists for RRR ph 3 The error in the duration of the MAP at 50% repolarization however is about the same at identical and different positions

The intraindividual variation (Table VI III) was calculated from all the recordings The S D for observations within one and the same individual is great The coefficient of variation is about 10% for the duration of the MAP at 90% repolarization and RRR ph 3 whereas it is about 18% for the duration of the MAP at 50% repolarization

Table V *Duration of MAP at 90% and 50% repolarization at different paced cycle lengths*
s=significant

Cycle length steps	Mean	S E	S D	*n*	Diff	*t*-dep(*n*−1)
At 90% repolarization						
800	263 6	8 6	39 6	21	13 0	6 18 (s)
↓ 700	250 6	8 5	38 8			
700	250 6	8 4	38 7	21	8 1	4 37 (s)
↓ 600	242 5	8 3	38 2			
600	257 3	9 5	36 9	15	6 2	5 07 (s)
↓ 500	251 1	9 0	34 8			
500	260 7	10 8	35 8	11	10 7	3 63 (s)
↓ 400	250 0	9 6	31 7			
At 50% repolarization						
800	161 2	4 6	21 2	21	6 7	5 38 (s)
↓ 700	154 5	4 6	21 1			
700	153 8	4 8	21 9	21	3 5	3 43 (s)
↓ 600	150 3	4 5	20 8			
600	156 5	5 2	20 1	15	5 4	5 40 (s)
↓ 500	151 1	5 3	20 7			
500	155 3	6 7	22 1	11	11 6	4 37 (s)
↓ 400	143 7	5 5	18 1			

The interindividual differences (Table VI IV) were calculated from the first recording in each individual The S D for the individual means expressed as coefficient of variation was about 15% for the duration values and more than 30% for the RRR ph 3

DISCUSSION

Earlier investigations have revealed an altered MAP configuration in various situations such as after physical training (4) altered thyroid state (8) and after electrical conversion in patients with atrial fibrillation (24) The method has also been evaluated in this clinic in different kinds of atrial arrhythmias (5) In order to evaluate the MAP of a single patient however there has been a need for reference material In this study we have attempted to obtain this by recording MAPs in healthy individuals

We investigated male volunteers only The results therefore may not be transferable to females as the sexes may differ in atrial repolarization Females have a different resting and maximal HR to males (2) and earlier investigations (4) have revealed a correlation between maximal HR and the duration of the MAP

With the present suction electrode technique for recording MAP (22) it is possible to determine the MAP in a simple pervenous way without serious complications The present MAP recordings are similar to those obtained by Olsson et al (22 23 24) The closeness of the electrodes minimizes influences of the superimposed atrial electrogram seen in other investigations (27) The configuration of the MAP in the present investigation is also in accordance with the observations on human atrial action potential recorded in vivo (3 28 30) using the microelectrode technique at open heart surgery Earlier investigations (7 14) comparing MAP to AP have demonstrated a close resemblance between the two methods during the entire repolarization phase

Earlier investigations on rabbits (25) and dogs (16 17) as well as in human heart (11 12 18 19) have demonstrated evidence of specialized con

Table VI *Sources of variation in the MAP variables during spontaneous sinus rhythm*

	Duration of MAP (msec)		
	50% repol	90% repol	RRR ph 3 (%/sec)
I Analysis	2 3 (1 4%)	2 5 (0 9%)	13 0 (3 2%)
II Position			
a) Identical	14 3 (8 6%)	2 6 (0 9%)	42 6 (10 3%)
b) Different	16 0 (9 8%)	14 1 (5%)	71 6 (17 6%)
III Intraindividual difference	28 6 (17 8%)	26 5 (9 8%)	44 2 (10 4%)
IV Interindividual difference	26 3 (16 4%)	35 7 (13 2%)	134 (31 5%)

ducting atrial fibers scattered between the contractile fibers. Durrer et al (9) on the other hand could not verify these findings and considered that impulses spread in a more or less concentric pattern from the sinus node. Action potential recordings from specialized fibers show a prominent overshoot and a prominent plateau (phase 2) whereas in the contractile fibers the plateau is missing. The present and earlier atrial MAP recordings show in most cases an appearance similar to that of the contractile element. In a few instances a distinct phase 2 similar to that of the specialized fibers has been recorded.

The P phase 0 duration during sinus rhythm represents the time for the spread of excitation from the sinus node through either contractile or specialized atrial fibers to the vicinity of the recording electrode. Therefore the duration of the P phase 0 interval is a measure of the distance of the MAP catheter from the sinus node. We were not able to detect any systematic change in the shape or the duration of the MAP in relation to the duration of the P phase 0 interval.

The amplitude of the MAP only represents a fraction of the transmembrane potential of the single heart muscle cell as judged from microelectrode studies (14). It is influenced by many factors (7) such as electrode-catheter characteristics. Another presumably important factor is the thickness of the subendocardial connective tissue layer in the [illegible]m. This proposition has received support from [illegible] work of Emslie Smith and Somers (10) in pa[illegible] with endomyocardial fibrosis. In our study no correlation was found between the amplitude of the MAP and the duration of the MAP phase 0 of the MAP or the RRR ph 3.

The duration of phase 0 has been difficult to calculate in some recordings. In such cases the end of phase 0 has been defined as the point at 90% depolarization where the MAP signal is clearly visible. This differs from the calculations made by Olsson (22) and explains the longer duration of phase 0 in the present study. It was possible in all recordings accurately to determine the start of the depolarization phase and in calculations using 90% repolarization as the end point the duration of the MAP will only be affected by a few msec. The diastolic level and thus the amplitude of the overshoot have in most recordings been uncertain and have not been calculated.

The duration of the MAP at 90% repolarization and to a lesser extent the RRR ph 3 show similar but more narrow limits than in the investigations by Olsson et al (22, 23, 24) on patients with various kinds of heart disease.

There are great intraindividual differences in the duration of the MAP and RRR ph 3. This variability within the same atrium, however, is accidental, i.e. there are no systematic changes when comparing a middle to a high position. Prinzmetal et al (26) used the duration of the action potential at 50% repolarization as an approximate measure of phases 1–2. In this study, however, the duration at 50% repolarization has been measured in order to calculate the RRR ph 3. The greatest interest, however, has been paid to the duration at 90% repolarization. The intraindividual differences in this variable are very small when identical positions of the MAP catheter are compared. This makes it possible to use the method in follow up studies in spite of the intraindividual variations (4).

With the present technique, placing of the MAP catheter is limited to relatively few positions within the atrium. Therefore it has not been possible extensively to map the atrium in order to ascertain differences in the shape and duration of the MAP at various points. Thus, we are unable to tell whether variations in MAP duration between two different sites in the same atrium occur abruptly or in a gradual fashion.

A possible explanation of this variation within the same atrium may be the non uniform distribution of vagal tone (1, 13) within the atrium. An unequal distribution of electrolytes within the atrium may also contribute to the variation (29). Also, we do not know to what extent the contractile and specialized fibers of the atrium contribute to the MAP within different parts of the atrium.

Microelectrode studies of electrophysiological changes in the rat atrium (6) have revealed an increase in the duration of the plateau phase and the duration of the action potential with age. In addition, the depolarization phase was slower with advancing age. The HR decreased with increasing age in a similar manner as in humans (2). An earlier study from this laboratory (4) demonstrated a good correlation between maximal HR and MAP duration—the lower the maximal HR, the longer the MAP. According to these data, one would expect an increased duration of the MAP in the older age groups. Age group 3 in the present study differed significantly from the other groups but in general

there was no age trend in the whole material These age differences have been neglected as there were no age differences when the RRR ph 3 the duration of the MAP and the cycle length were correlated No obvious reasons such as the degree of physical fitness (4) electrolyte abnormalities (15) or thyreoid dysfunction (8) were found to explain the discrepancy between the results in age group 3 and the other groups

Monophasic action potential—cycle length

Earlier investigations on heart muscle cells (15) and in vivo (22) have revealed a correlation between preceding cycle length and the duration of the MAP in that the shorter the cycle length the shorter the duration of the MAP The present investigation is in accordance with this finding In our study the reduction of the duration of MAP in relation to the reduction of cycle lengths is somewhat less pronounced than in the above studies This might partly be due to the great intraindividual differences both with regard to initial durations and response to altered HR The average decrease in duration of the MAP for a decrease in cycle length of 100 msec is about 10 msec both in spontaneous sinus rhythm and during atrial pacing

The present method does not offer possibilities of mapping the entire atrium because of the difficulties in getting a proper position of the MAP catheter Thus only occasionally has it been possible to discover slow phase 4 depolarization (22) or other factors besides a short duration of the MAP which might be arrhythmia provoking in patients

The aim of this study is to provide reference material for further investigations concerning the distribution and variation of the different MAP variables within the same atrium in sinus rhythm as well as at different pacing frequencies With the present technique it is possible to evaluate the MAP of the right atrium during the repolarization phase whereas the depolarization is more difficult to judge Good correlation has been shown in the present material between the duration of the MAP at 90% repolarization and the effective refractory periods of the right atrium This will be further detailed in a forthcoming publication

ACKNOWLEDGEMENTS

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With the present technique placing of the MAP catheter is limited to relatively few positions within the atrium Therefore it has not been possible extensively to map the atrium in order to ascertain differences in the shape and duration of the MAP at various points Thus we are unable to tell whether variations in MAP duration between two different sites in the same atrium occur abruptly or in a gradual fashion

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Atrial Repolarization in Healthy Males

Studies with Programmed Stimulation and Monophasic Action Potential Recordings

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ABSTRACT Right atrial effective refractory periods (AERP) and monophasic action potentials (MAP) have been determined in 29 healthy males in four different age groups between 25 and 64 years One age group (45–54 years) showed a significantly longer AERP than the others, with a mean of 283 msec compared with 230–238 msec in the other groups However, no age trend was found in the total material The AERP decreased at higher paced heart rates, the decrease between paced cycle lengths of 800 and 600 msec amounting to 13 msec When the MAP and the AERP were determined in the same position of the atrium, they showed no statistically significant correlation A possible explanation is that the cells contributing to the AERP and the MAP are not altogether the same The MAP and the AERP determinations have a similar degree of reproducibility but possibly mirror different kinds of repolarization phenomenon

The relationship between the action potential (AP) and the refractory state of the single heart muscle cell has been evaluated using microelectrode technique The effective refractory period has been shown to end at about −60 mV during the repolarization phase (15) Using the extra stimulus technique it is possible to determine accurately the effective refractory period in different positions in the human heart (24) It is also possible to evaluate the repolarization of the heart muscle from recordings of the monophasic action potential (MAP) (20 21 23) The MAP mirrors the AP in a number of cells (9 16) probably in different states of refractoriness

The aim of the present study was to obtain a reference material of right atrial effective refractory periods (AERP) in healthy males and to compare the two above mentioned measures of atrial repolarization The age dependence of AERP has also been evaluated

MATERIAL AND METHODS

Twenty nine healthy male volunteers participated in the study The procedure was fully explained to all individuals and all gave their informed consent The Ethical Committee of the Medical Faculty had reviewed the procedure and approved the design of the study All subjects but one (no 56) also participated in an investigation of right atrial MAP described elsewhere (4) The relationship between MAP and AERP in the same site of the atrium (see below) was calculated from a second recording after physical training in 8 of the 29 individuals (3) The case numbers in the present tables correspond to those presented in the previous investigations

The participants in the study were all healthy as judged from the history physical examination ECG and chest X ray They had no electrolyte abnormalities on the day of investigation They were divided into four age groups group 1 25–34 years (mean 29) group 2 35–44 (mean 40) group 3 45–54 (mean 48) and group 4 55–64 years (mean 58)

The MAP was determined using the suction electrode technique as described previously (4) The position of the MAP catheter varied between recordings and individuals (Table I) The variables used in the calculations were the duration of the MAP at 50% and 90% repolarization and the relative repolarization rate during phase 3 (RRR ph 3) In the 8 persons in whom pacing was performed via the MAP catheter the interval from the start of phase 0 of the MAP to 70% repolarization was also calculated (Table II) In the majority of cases the MAP was also used to detect the propagated impulse in connection with the determination of the AERP

AERP was determined using the extra stimulus method as described by Ryden et al (24) Right atrial pacing was performed by means of a bipolar pacemaker electrode catheter which was positioned near the sinus node in the majority of cases In 8 subjects AERP was determined by pacing through the MAP catheter

The pacemaker output was adjusted to double the diastolic threshold for stimulation A specially constructed pacemaker (Siemens Elema AB Sweden) was used for pacing and the delivery of premature stimuli The pacemaker produced square wave impulses with a duration of 2 msec and of constant current The basic cycle length had a precision of +1 msec and the premature

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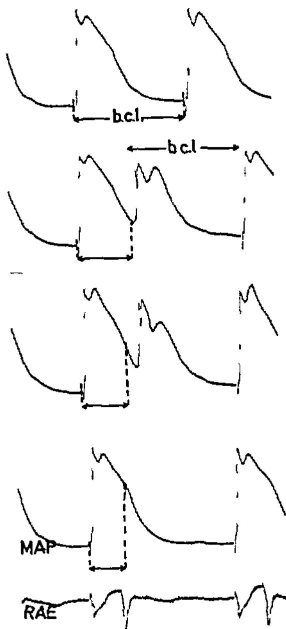


Fig 1 Determination of AERP with the extra stimulus technique using the MAP electrode for detecting the propagated impulse *b c l* =basic cycle length *RAE*= right atrial electrogram The successive decrease in coupling intervals is indicated by arrows

RESULTS

The results of the individual determinations of AERP and MAP are shown in Table I The recordings in which pacing was performed via the MAP

Table III *Mean values S D and S E M in the four age groups at a paced cycle length of 800 msec*
Group 3 differs significantly from the other groups F (3 17)=4 07

	Age group			
	1	2	3	4
n	5	4	8	4
Mean	238	230	283	237
S D	30 1	27 9	26 4	40 4
S E M	13 5	13 9	9 4	20 2

catheter are presented in Table II The results of the two techniques have been separated in the further calculations and presentations

AERP–heart rate

In six recordings AERP was determined with the pacemaker catheter in the same position at both 600 and 800 msec It will be seen from Fig 1 that the AERP increased with increasing cycle length The mean increase between 600 and 800 msec was 13 msec The increase was significant as tested by the t test of paired differences (t=2 8974)

AERP–age

The individual AERP values are given in Table I The analysis of differences between the means of the different age groups was performed by one way analysis of variance using the F ratio (F) as test variable Because of the small numbers of recordings no analysis of age dependence was performed at a paced cycle length of 600 msec but age group 3 differed significantly from the other groups at a paced cycle length of 800 msec (Table III) There were however no progressive trends between the four groups according to age

The relationship between age and the different MAP variables had been determined previously in a larger group of healthy males including the present subjects These results have been presented in detail elsewhere (4)

AERP–MAP in the same site of the atrium

The results of the analyses in 8 subjects in whom pacing was performed via the MAP catheter immediately after MAP recording at the same paced cycle length are shown in Table II

The relationship was analysed by linear regression There was no significant correlation between

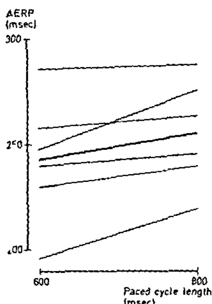


Fig 2 Relationship between AERP and paced cycle length in six patients The mean increase is indicated with a thick line

the AERP and any of the MAP variables used in these subjects (Fig 3) The AERP varied between −65 and +19 msec of the duration of the MAP at 90% repolarization

AERP–MAP at different sites of the atrium

e results obtained by pacing via the pacemaker eter in one position of the right atrium and ording the MAP in another position are shown in able I

The relation between the different MAP variables (Y) and AERP (Y) was analysed by linear regression The correlation coefficients (r) were tested by

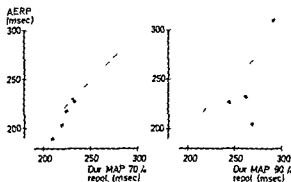


Fig 3 Relationship between AERP and the duration of MAP at 70 and 90% repolarization in the recordings in which AERP was determined via the MAP catheter The line of identity is indicated

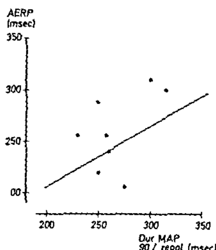


Fig 4 Relationship between AERP and the duration of MAP at 90% repolarization The regression line is indicated

the t test (t_r) The comparison was performed at cycle lengths of 800 and 600 msec The relationship between AERP and the duration of the MAP at 90% repolarization at a paced cycle length of 800 msec was statistically significant ($p<0.01$) (Fig 4) The regression line was $Y=89.0+0.5875X$ ($r=0.62$ $t_r=3.12$ $S_{yx}=29.9$) The correlation was not significant at a paced cycle length of 600 msec The relation between the AERP and the duration of the MAP at 50% repolarization was not significant either at a paced cycle length of 800 or at 600 msec

A correlation was found between AERP and RRR ph 3 in that the higher the RRR ph 3 the shorter the

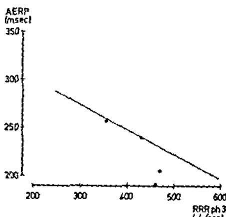


Fig 5 Relationship between AERP and the relative repolarization rate during phase 3 (*RRR ph 3*) The regression line is indicated

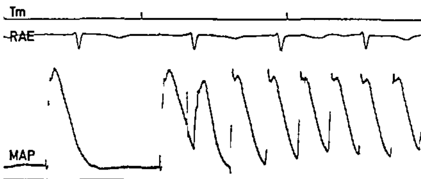


Fig 6 AERP determination resulting in atrial flutter in one of the individuals (no 38) *Tm* = time marker

AERP The regression line was $Y=351\ 6-0\ 2566\ X$ ($r=0\ 60$ $t=3\ 04$ $S_{yx}=30\ 2$) at a cycle length of 800 msec (Fig 5) and $Y=414\ 1-0\ 3927\ X$ ($r=0\ 65$ $t=2\ 39$ $S_{yx}=41\ 2$) at 600 msec

Statistical analysis

The interindividual differences in AERP were calculated from the recordings at a paced cycle length of 800 msec The S D for the individual means expressed as coefficient of variation was about 13% at this cycle length The reproducibility in determining the AERP has been tested by Rydén et al (24) using exactly the same technique as in the present study The result of duplicate determinations showed an error of a single determination according to the formula $s=\sqrt{\Sigma d_i^2/2n}$ (d_i=difference between two analyses n=no of pairs) and transformed to a coefficient of variation of 0 8% As shown in our previous investigation (4) the reproducibility of the MAP recordings was of the same magnitude when identical positions of the MAP catheter in the atrium were investigated (0 9% for the duration at 90% repolarization) The inter and intraindividual variation was considerable however (9 8–13 2% at 90% repolarization)

Side effects

In connection with manipulation of the catheter some ectopic beats were seen During AERP determinations short runs of supraventricular ectopics were observed relatively often when the coupling intervals approached the AERP

Four of the individuals developed atrial fibrillation and one individual atrial flutter during AERP determination (Fig 6) Four subjects were electroconverted while one reverted to sinus rhythm spontaneously

DISCUSSION

The refractoriness of a single heart muscle cell has been subdivided into four periods according to Hoffman and Cranefield (15) During the first period effective refractory period (ERP) no propagated impulse can be evoked The next period (relative refractory period) starts when strong stimuli produce a propagated impulse but after a long period of latency This is followed by a brief interval during which the threshold for stimulation is slightly lower than in the resting cell (supernormal period) The following period is called full recovery time If the refractoriness is compared with the state of the cell as determined by its action potential (AP) it is found that the ERP ends when the transmembrane potential is about −60 mV (15) This would correspond to 70–75% repolarization of the AP At this level only strong stimuli are able to evoke a propagated impulse When determining the ERP of the human heart in situ however only stimuli twice the diastolic threshold level are used for safety reasons (8) If stimuli twice the threshold strength had been used in single heart muscle cells the ERP would probably have been at least 15 msec longer as judged from strength interval curves (17) and would correspond to 80–90% repolarization of the AP Following a change in heart rate it takes some time before the refractory period is stable (17) Most of the adaptation has occurred within 30 sec Errors due to this stabilizing process were avoided by pacing for at least 30 sec before the first extra stimulus was delivered A premature beat also has some influence upon the refractoriness of the next few beats of the basic heart rate (17) This source of error was avoided by allowing at least ten consecutive beats of the basic cycle length between each extra stimulus The strength of the extra stimulus greatly influences the duration of the re-

fractory period (17) In all cases a thorough determination of the stimulation threshold was performed before AERP was determined and the stimulus strength was always double the threshold level

AERP–heart rate

Previous studies of human atrium have shown a decreased duration of AERP with increasing heart rate (6 10 12 18 24) It is difficult to compare the results directly but the degree of change in AERP in our study with regard to rate is similar to that found in the above investigations The degree of shortening of AERP at higher heart rates in our investigation is similar to the degree of shortening in the duration of the MAP between corresponding heart rates (4)

AERP–age

Comparisons of cardiac refractory periods between children (11) and adults (10) have shown a shorter AERP in children their mean AERP being 196 msec and that of adults 239 msec In the latter investigation however the ages of the adults ranged between 15 and 77 years and no subdivision of the adults was made according to age Within this latter group no age dependence was found concerning AERP but the material was rather small

Age group 3 (45–54 years) in the present study had a significantly longer duration of the AERP [illegible] the other age groups There was however no progressive trend in our material according to age In an investigation of right atrial MAP in healthy males of different ages including the present subjects (4) the duration of the MAP was significantly longer in age group 3 There was no progressive trend according to age in that study either In the MAP investigation clear age differences were found only during spontaneous sinus rhythm not during atrial pacing

In previous investigations (7 10 18) the AERP has been determined in patients with different heart diseases and on different drugs which might have influenced the results The ages of patients have varied considerably One investigation (18) showed a mean AERP of about 310 msec determined at varying paced cycle lengths The mean age was about 52 years Another study (7) also showed considerably longer AERPs (mean 277 msec) than our investigation On the other hand Denes et al (10) found AERPs similar to those obtained in the present study but their two patients older than 70 years had very long AERPs In all the studies quoted the interindividual variation in AERPs was substantial It is possible that the prolongation of AERP and right atrial MAP in age group 3 might be due to chance but the relatively small number of recordings in age group 4 may have made it impossible to detect any progressive age trend

MAP–AERP in the same site of the atrium

In 8 recordings the AERP was determined by pacing through the MAP catheter after MAP recording in the same position of the atrium In these cases no significant correlations were found between AERP and any of the MAP variables This might be due to the few investigations performed On the other hand the AP of the single heart muscle cell and the MAP of a number of cells need not show the same relationship to refractoriness The MAP signal is probably a synthesis of the APs in a number of cells and it is probable that the refractory state of the tissue from which the MAP is recorded is determined by the course of cells with the shortest refractory periods and most rapid conduction properties Thus the cells that determine the value of the AERP are probably not altogether the same as those that determine the configuration of the MAP It is well known that the duration of the AP differs between closely adjacent cells (5 14 19) The refractory state also differs between adjoining cells (1 19) It is possible that small changes in catheter position change the composition of the cells contributing to the AERP and thus the value of the AERP without necessarily affecting the general configuration of the MAP

It is not known to what extent the suction influences the AERP The AP is probably not changed The comparison MAP–AERP in the same site of the atrium was performed in well trained subjects (3) It is not known whether physical training can alter the relationship between MAP and AERP

Summarizing the results it is only possible to draw rough conclusions about the AERP from the duration of the MAP at least when AERP is determined via a suction electrode catheter

AERP–MAP at different sites of the atrium

In all but 8 of the recordings the AERP and right atrial MAP were determined at different positions within the atrium As those variables showed great intraindividual variations according to duration it

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Significance of Cardiac Arrhythmias Preceding First Cardiac Arrest in Patients with Acute Myocardial Infarction

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ABSTRACT In 417 consecutive cases of acute myocardial infarction (AMI) within a minimum of 21 days stay in the Coronary Care Unit (CCU), primary cardiac arrest occurred in 41 patients (9 9%), the first episode occurring during ECG monitoring in 24 patients After cessation of ECG monitoring, and within 2–25 days after admission, it occurred in 17 patients Cardiac arrhythmias before the first cardiac arrest were analysed in these two groups of patients, and compared with the occurrence of cardiac arrhythmias within the first 5 days in 100 consecutive patients with AMI without complicating cardiac arrest No significant difference in the frequency of cardiac arrhythmias could be demonstrated between the two groups with cardiac arrest and the control series Moreover, complete absence of rhythm disturbances right up to the beginning of cardiac arrest was as frequent in the patient groups as in the control series (around 20%) As there is not sufficient evidence that treatment with antiarrhythmic drugs can provide safe prophylaxis against the occurrence of cardiac arrest, it is concluded that all patients with AMI should be kept in the CCU and monitored by cable or by telemetry, for the duration of their stay To achieve this, the cost in financial terms manpower and reorganization is not a deterrent Furthermore, this study does not give any support to the usual practice of confining possible attempts of prophylactic antiarrhythmic treatment to patients with arrhythmias of certain frequencies and/or types

It is well known that the risk of sudden cardiac arrest in acute myocardial infarction (AMI) is greatest by far during the first hours and days of the disease This complication however is by no means confined to the earliest stages of the AMI In our experience about one third of all first episodes of cardiac arrest occur later than five days after the onset of AMI (14) As most coronary care units (CCU) are dimensioned to monitor patients for only a few days or to monitor only a fraction of those with AMI considerable interest has been attached to the possibility of foreseeing and preventing cardiac arrest which usually means ventricular fibrillation Some authors suggest that ventricular fibrillation not preceded by ventricular tachycardia is an uncommon event in these patients (7) In other series cases of ventricular fibrillation have been observed either with no preceding arrhythmia or with arrhythmias of such short duration that there was hardly time for prophylactic treatment (1 4)

These problems are still incompletely elucidated mainly because the possibilities for observing and registering data tend to be limited but also because the principles for selecting patients for a CCU are not uniform

The purpose of this investigation has been to evaluate the occurrence of cardiac arrhythmias as a warning of cardiac arrest in an unselected series of patients with AMI who were observed continuously during their stay in hospital i e for a minimum of 21 days for all surviving patients

MATERIAL AND METHODS

The basic material is a consecutive unselected series of 417 patients with confirmed AMI representing all patients admitted to the CCU in Copenhagen County Hospital Glostrup with this diagnosis during a period of 1½ years (Apr 1969–Oct 1970)

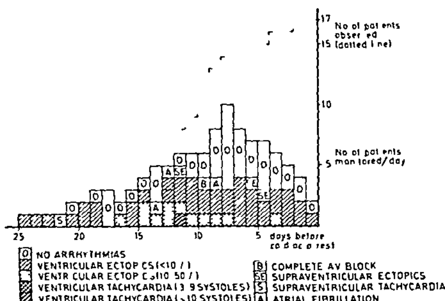


Fig 1 Cardiac arrhythmias in 17 patients with AMI who had their first cardiac arrest after the cessation of ECG monitoring

The diagnosis of AMI rests on the finding of at least two positive out of the three symptoms and signs typical history typical pattern and course of ECG changes and typical rise and course of the serum enzymes in the fatal cases further confirmed by the post mortem finding of a fresh myocardial infarction The diagnostic criteria are based on the recommendations from WHO (18) and described in further detail in another paper (15) From the present analysis we have excluded all patients with severe cardiac insufficiency and with cardiogenic shock persisting in spite of adequate treatment even if during such complication a (secondary) cardiac arrest occurred The series analysed here thus comprises all patients with primary cardiac arrest observed during this period

Cardiac arrest during ECG monitoring was observed in 24 patients by the occurrence of ventricular fibrillation treated by DC defibrillation (21 patients) or by the occurrence of asystole treated by cardiac massage and ventilation and intracardiac injection of cardiac stimulants (3 patients) Spontaneous reversion of ventricular fibrillation after up to 30 sec duration was observed in one patient who also had episodes of treated cardiac arrest and the spontaneous ventricular fibrillation has been classified among the ventricular arrhythmias as described below

Cardiac arrest outside ECG monitoring was observed in 17 patients by the sudden occurrence of unconsciousness and pulselessness One of them was defibrillated without ECG control and woke up after which ECG showed sinus rhythm ECG showed ventricular fibrillation in 9 asystole in 5 and atypical ECG activity without evidence of pumping function in 2

In another 26 patients cardiac arrest had started outside the CCU in most cases out of the hospital These patients are included in the series of 417 patients but not in the analysis of the preview to cardiac arrest mentioned below

During the period of investigation the CCU consisted of 8 monitored plus 13 unmonitored beds the number of the latter being extended as required Patients with confirmed AMI were monitored for an average of 7 days until they were transferred to an unmonitored bed unless arrhythmias or other complications necessitated further monitoring During the whole stay the patients remained within the same ward and under the care of the same nursing staff

All monitored ECG curves were recorded continuously on magnetic tape 24 hours a day The analysis of cardiac arrhythmias in this series is based on observations and recordings made during the routine playback of these tapes

The classification of arrthythmias observed in the analysis appears from Figs 1 and 2 and from Table I Each patient is represented by one type of arrhythmia only The occurrence of complete AV block in a few cases was given priority over simultaneous occurrence of ventricular ectopics but in all other instances ventricular arrhythmias were listed prior to all other kinds of rhythm disturbances If more than one type of ventricular arrhythmia was observed the most frequent or most "serious" according to the sequence in Fig 1 was registered

Detailed analysis of all cardiac arrhythmias during ECG

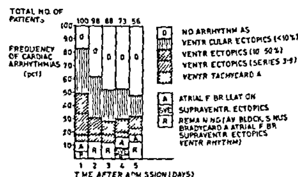


Fig 2 Cardiac arrhythmias in 100 patients with AMI without complicating cardiac arrest

Table I *Cardiac arrhythmias during ECG monitoring before first episode of cardiac arrest in 24 patients with AMI*

Days before															Cardiac arrest
15	14	13	12	11	10	9	8	7	6	5	4	3	2	1	
														0	VF
														0	VF
														0	VF
														0	VF
														0	VF
										V4	V1	0	0	S2	VF
														V1	VF
													V1	V1	VF
														V2	VF
													V2	V2	VF
														V3	VF
														V3	VF
														V3	VF
0	0	0	0	0	0	0						V1	V	V3	VF
														V4	VF
														V4	VF
														V4	VF
				0	V2	0	V1	V1	0	VF	AF	0	AF	VF	VF
														AV	VF
														AV	VF
														AV	VF
														0	AS
							V2	0	0	V1	V1	V1	V2	0	AS
				V1	0	0	0	0	0	0	0	0	S1	0	AS

0 no dysrhythmias of the following types. AF atrial fibrillation (intermittent). S1 supraventricular extrasystoles. S2 supraventricular tachycardia. V1 ventricular extrasystoles <10%. V2 ventricular extrasystoles 10–50%. V3 ventricular tachycardia 3–9 ectopics in succession. V4 ventricular tachycardia >10 ectopics in succession. VF ventricular fibrillation with spontaneous recurrence. AV complete AV block.

monitoring was made in the following three groups of patients. 1) The 24 patients who had their first episode of cardiac arrest during ECG monitoring. 2) The 17 patients who had their first episode of cardiac arrest after leaving ECG monitoring. 3) The first 100 consecutive patients without complicating cardiac arrest during the stay in the CCU.

Statistical calculations have been made by means of the χ^2 test with Yates' correction.

RESULTS

Twenty four patients with cardiac arrest during ECG monitoring

As appears from Table I, the cardiac arrest was ventricular fibrillation in 21 patients, asystole in 3.

Within the last 24 hours before cardiac arrest monitoring in 5 of the 21 patients with ventricular fibrillation showed no disturbances in cardiac rhythm apart from a short ventricular tachycardia immediately preceding the ventricular fibrillation in 3 patients, lasting for 6, 7 and 27 sec, respectively. One patient had an attack of supraventricular tachycardia lasting for 10 min before the ventricular fibrillation. Four other patients had single beats of ventricular extrasystoles of different frequency within one or two days before cardiac arrest. In 7 patients attacks of ventricular tachycardia of various duration were observed before ventricular fibrillation, in 2 of them 10 min and 42 min before the episode, but in the other 5, 1–15 hours before ventricular fibrillation. One additional patient had attacks of ventricular fibrillation which reverted spontaneously after 12 and 22 sec duration, 5 days and 3 min before the cardiac arrest. The remaining 3 patients of the 21 with ventricular fibrillation had pacing catheters placed intracardially when the ventricular fibrillation occurred, both with the pacemaker set on demand and with no evidence in the ECG curves that any erroneous impulse c[illegible] be responsible. Mechanical irritation by the catheter tip, however, could not be excluded as e[illegible] factor in these three instances.

the CCU does not mean an increase in the total number of beds in the hospital merely a rearrangement within the Department of Internal Medicine or Cardiology The size of the nursing staff does not need to be increased much (still less than one person per patient) and the cost of the telemetric equipment is very reasonable (approximately Dcr 30000 per patient for transmitter+receiver+ warning unit) The therapeutic results from this arrangement as compared with those described here are presented elsewhere (15)

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The Sick Sinus Syndrome

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ABSTRACT Clinical and electrophysiological characteristics have been investigated in a group of 30 patients with a sick sinus syndrome No predictable response to exercise or drugs was observed, although a poor response of the sinus rate to atropine was present Distal conduction abnormalities were found in seven of 14 patients, in whom detailed electrophysiological measurements were made, and sinus node recovery time was abnormal in all except one Treatment with permanent pacing not only relieved syncope and dizziness, but made drug treatment of associated tachyarrhythmias feasible The elusive and intermittent nature of the syndrome is stressed The pathological findings in one case are described at length

Sudden impairment in cardiac conduction or impulse formation may lead to a variety of cerebral symptoms and ultimately to syncope Since 1967 when Lown (16) coined the term sick sinus syndrome an increasing number of patients with abnormal sinus node function has been reported (9 25 27) in whom sinus bradycardia sinus arrest or sinoatrial block sometimes alternating with atrial tachyarrhythmias were the dominant symptoms which required treatment

Its intermittent character which often produces symptoms resembling transient ischemic attacks or epileptic seizures repeatedly eludes detection while alternating brady and tachycardia may pose therapeutical dilemma s

We observed 30 patients with symptomatic sinus node disease fulfilling the criteria of a sick sinus syndrome These patients exhibited 1) severe persistent sinus bradycardia 2) episodic sinus arrest or sinoatrial block often without escape rhythm 3) sinus bradycardia with paroxysmal atrial fibrillation flutter or tachycardia Our clinical experience and an approach to a more precise evaluation of the syndrome are reported

PATIENTS AND METHODS

A group of 30 patients 10 men (aged 53–81) and 20 women (aged 45–88) with symptomatic sinus node disease was observed in 1967–74 Both patients below 50 years were women one with the familiar form of this syndrome Patients with acute myocardial infarction (AMI) or sinus node dysfunction caused or aggravated by drugs were excluded In a number of these patients the effects of exercise and drugs on their symptoms were studied Atropine was given either 2 mg i m or 1 mg i v and heart rate was registered for one hour isoprenaline was given sublingually (10–20 mg) and the same procedure was done during two hours Bicycle ergometer tests with a load of 50 W were performed until exhaustion

Electrophysiological investigations were made by intracardiac ECG Using the Seldinger technique two catheters were introduced in the right femoral vein a tripolar catheter no 7 was positioned against the lateral wall of the right atrium and a bipolar electrode wire with electrodes 1 cm apart in the His bundle region as described by Scherlag et al (26) Standard leads I II and III a unipolar high atrial ECG and a His bundle ECG were recorded on an 8-channel Elema at a paper speed of 100 mm/sec Intra atrial conduction was measured from the beginning of the P wave in lead II of the surface ECG to the first atrial depolarization as seen in a low atrial recording made from the bipolar catheter for His bundle recording (PA interval) Atrioventricular conduction was measured as AH time (atrial depolarization to His spike) HV time (His spike to beginning of ventricular depolarization on the surface ECG) and HS time (His spike to the end of ventricular depolarization) Sinoatrial recovery time (SART) was measured after pacing the right atrium for 20 sec with 120 beats/min The interval between the last paced beat and the first sinus beat was measured and the average of five measurements was taken as the SART

Atrial pacing was used with increments of 10 beats/min to determine the rate at which a Wenckebach phenomenon of the AV node was recorded and the rate prior to this was designed as the Wenckebach point In some of these patients not every parameter was obtained because of

Table I *Age duration of complaints and possible etiology in 30 patients with the sick sinus syndrome*

Females	20
Males	10
Age (y)	
<50	2
50–60	2
60–70	3
70–80	17
80–90	6
Duration of complaints before diagnosis (y)	
<1	20
1–5	8
>5	2
Etiology	
Angina pectoris	11
Myocardial infarction	6
Hypertension	2 (4)*
Diabetes mellitus	1 (2)*
Hypothyroidism	(1)*
Hyperthyroidism	1
Familial	2
Unknown	7

* No of patients who also had coronary heart disease

arrhythmias during the study In view of the varying duration of the arrhythmia we have not sought a correlation between the type of complaint (syncope or dizziness) and the existence of a brady or a tachyarrhythmia

In 27 patients a permanent transvenous pacemaker was implanted and all patients were followed for at least one year as outpatients at two-month intervals

RESULTS

Age sex and etiology The majority of patients were elderly and female and had a short history of complaints (Table I) In 17 patients definite evidence of coronary heart disease was present either as a prior well documented infarction or as unequivocal angina pectoris Coronary arteriography was not performed A quarter of the patients had hypertension in two patients the syndrome was familial three patients had diabetes mellitus one hyperthyroidism and one hypothyroidism both well controlled In the remaining patients no clear cause could be identified There were no cases of myocarditis

Symptoms Syncope or attacks of dizziness were the most prominent symptoms in 22 patients while tachyarrhythmias were the major abnormality in 8 (Table II) In all cases the cause of the dizziness was documented by long term monitoring In three patients the persistent bradycardia contributed to their congestive heart failure while drug treatment of tachycardias aggravated the alternating brady arrhythmia in six

Table II *Major signs in 30 patients with a sick sinus syndrome*

Sinus bradycardia	
<45/min	9
45–60/min	1
Sinoatrial block or sinus arrest (7 with syncope)	12
Brady tachyarrhythmias (with palpitations dizziness and heart failure)	8

Initially a large number of patients was thought to have transient cerebral ischemic attacks chiefly due to the intermittent character of their arrhythmia and cardiac monitoring for prolonged periods was necessary to identify the cause of their symptoms

ECG findings In 10 patients the major ECG finding was episodic sinus bradycardia in 2 cases combined with marked sinus arrhythmia In 12 patients 7 of whom experienced a syncope sinoatrial block or episodic sinus arrest were observed Nodal or ventricular escape rhythms appeared after prolonged arrest or were absent while in others tachy arrhythmias were followed by sinus arrest In 8 patients the bradycardia alternated with symptomatic attacks of supraventricular tachyarrhythmias always atrial fibrillation or flutter (Table II) Short episodes of supraventricular tachycardia were seen in 4 more patients but only one ventricular tachycardia A number of associated disturbances of rhythm and conduction were seen in 15 patients they were suggestive of defects in the atrioventricular node or the distal section of the ventricular conduction system (Table III)

Table III *Associated ECG findings in 30 patients with the sick sinus syndrome*

Right bundle branch block	4
Left bundle branch block	5
Right bundle branch block with marked left axis deviation	1
First degree AV block	2
Second degree AV block	1
Atrioventricular dissociation	2
Ventricular tachyarrhythmia	1

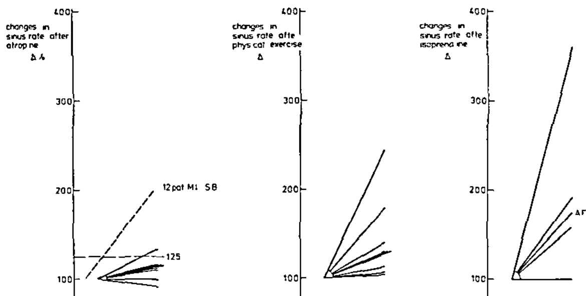


Fig 1 Percentage changes in sinus rate after various stimuli in patients with sick sinus node syndrome

Effects of drugs and exercise (Fig 1) Eight patients with sinus bradycardia (heart rate <50/min) were given atropine In 7 of them the peak heart rate achieved was less than 25% of the control value none of them attaining a sinus rate above 90 beats/min Five patients were given 10–20 mg isoprenaline sublingually No predictable effects on sinus rate were observed in one patient atrial fibrillation with a high ventricular rate occurred while in another sinus rate barely increased In 9

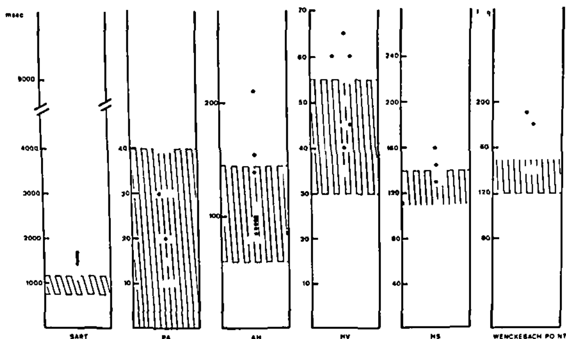


Fig 2 Electrophysiological data in 14 patients with sick sinus syndrome Normal ranges are hatched



Fig 3 (A) Gross aspect of the opened aortic valve The valve itself shows slight senile changes The coronary ostia (arrows) are markedly narrowed by atherosclerotic depositions in the aortic intima

(B) Posterior view of the heart after removal of both atrial chambers The right coronary artery is dominant and shows three aneurysms (*) The sinus node artery originates immediately distal to the most proximally located aneurysm (arrow) AO=aorta

(C) Gross aspect of the endocardial aspect of the opened right atrium The gray discoloration is due to extensive fibrosis of the atrial myocardium which involves the septum and the greater parts of the anterior and posterior walls including the crista terminalis The area of the sinus node (arrows) is also severely fibrosed *SVC*=superior vena cava

(D) The sinus node (*SN* between arrows) shows extensive fibrosis with almost total replacement of muscular elements The sinus node artery is embedded in the node and is in this location virtually normal Elastic tissue stain ×14

(E) A high power view of the sinus node reveals that only a few specialized cells remain among extensive fibrosis Elastic tissue stain ×350

elderly patients bicycle ergometer tests were performed Again the effects on sinus rate were variable ranging from significant increase to minimal change in basic rate

Electrophysiological studies In 14 patients intracardiac studies were made of conduction and impulse formation As shown in Fig 2 SART was significantly prolonged in 8 of 9 patients This prolongation was however mostly moderate despite long periods of sinus arrest during clinical observation In 3 patients this interval was measured again after 2 mg atropine i m and a return to normal was observed in only one patient Intra atrial conduction was normal in the 12 patients studied Conduction through the atrioventricular node was delayed in 2 patients as demonstrated by a prolonged AH interval while 3 showed a Wenckebach phenomenon at a paced rate below 120 beats/min In 5 of 13 patients distal conduction through the bundle branches was delayed as reflected in a prolonged HV interval while in 7 of 13 patients total distal conduction as measured by HS time was prolonged When there was a prolonged HV time a bundle branch block was always found on the surface ECG

Treatment

In 26 of the 30 patients a permanent transvenous ventricular pacemaker was implanted 19 of the on demand type and 7 fixed rate pacemakers Indications were syncope (12 patients) dizziness (9 patients) and bradycardia enhanced by drug treatment of supraventricular tachycardias (5 patients) Four patients were not given a pacemaker initially In one patient tachycardias could be controlled by quinidine two had only minor symptoms during follow up and one patient finally needed a pacemaker for syncope Of the 21 patients with cerebral symptoms all except one were greatly improved by permanent pacing All patients were followed as outpatients at two-month intervals until now During the observation period 4 patients died from atherosclerotic heart or brain disease

In the 5 patients with chiefly supraventricular arrhythmias treatment with digoxin quinidine or β blocking agents was facilitated by continuous cardiac pacing since further suppression of sinus node function was compensated for by the pacemaker Two patients who had been hospitalized for months while being treated for their arrhythmias with drugs without permanent effect became symptom free as a result of this combined approach

Pathological findings

A post mortem was performed in one of the 4 patients who died The important pathological findings

were confined to the cardiovascular system There was extensive atherosclerosis which had led to narrowing of both coronary ostia (Fig 3A) and severe involvement of both coronary arteries The right coronary artery showed three atherosclerotic aneurysms (Fig 3B) and multiple narrowings while the left circumflex artery and the left anterior descending artery showed obliterative lesions in their proximal segments The lumen inside the aneurysms was extremely narrowed by thrombosis though each was still patent The sinus node artery originated from the right coronary artery immediately distal to the first aneurysm (Fig 3B) but showed no obliterative lesions The atrioventricular node artery had its origin in the dominant right coronary artery at the level of the crux cordis The right atrium showed extensive fibrous replacement of the myocardium of the greater part of the atrial septum the anterior and posterior atrial free walls and the crista terminalis (Fig 3C) The sinus node also showed extensive fibrosis (Fig 3D) The atrioventricular node however was not significantly altered The left ventricle showed two scarred myocardial infarcts One of them was located in the apex of the left ventricle and had resulted in a small aneurysm partly filled with thrombus and the other in the postero-basal region of the left ventricle

DISCUSSION

Sinus node dysfunction is being increasingly diagnosed in the ageing population through improved monitoring facilities and may explain certain cerebral ischemic episodes as manifestations of cardiogenic neurology (1) Since permanent pacing offers effective treatment (4 21) correct diagnosis is important During the period of this study 15% of all pacemakers in our department were implanted for sinus node dysfunction

Manifestations of the sick sinus syndrome may be intermittent and sinus bradycardia in the elderly is not diagnostic per se (3) Many diagnostic procedures have been advocated but are often non specific and therefore unhelpful Some patients may react to carotid sinus massage by excessive slowing or abrupt sinus arrest (17) but again this is not a typical response

Atropine Administration of atropine is more useful since in normals or in patients with AMI and sinus bradycardia the sinus rate increases 50% to an average of 100 beats/min after atropine either 1 mg i v or 2 mg i m (2 5) In 12 patients with AMI and sinus bradycardia we observed a maximal increase of 105% after 2 mg atropine i m while all patients achieved a rate of more than 90 beats /min (7) A markedly depressed response to a standardized dose of atropine may thus point to the diagnosis When tested none of our 8 patients reached a heart rate above 90 beats/min

SART Some authors (17 19) found the measurement of the SART after overdrive suppression by atrial pacing a discriminating test and in one series an abnormal response was found in 29 out of 31 patients This test however reflects only momentary sinus node function and may be normal when pacing stimuli delivered to the atrium fail to penetrate the sinus node through an entrance block (10 11) this being thought responsible for normal results in a third of the patients (8) In 3 patients with only slight prolongation of their SART clinically long periods of sinus arrest were observed

Monitoring Long term monitoring is most likely to document the existence of sinus node dysfunction Careful examination of the onset and cessation of tachyarrhythmias will often reveal defects in sinus node impulse formation Tachycardia may appear after prolonged sinus arrest or by overdrive suppression evoke a sinus bradycardia upon termination Marked sinus bradycardia may develop after drug treatment or cardioversion of arrhythmias especially atrial fibrillation (16)

Treatment The remarkable finding of associated conduction defects up to 60% in a large series (18) may partly explain the absence or delay of escape rhythms They were present in half our patients His-bundle electrography in these cases had no clinical significance except for the type of treatment Distal conduction disturbances were discrete but because of the uncertainty about possible progression of these disturbances implantation of an atrial pacemaker seemed undesirable The implantation of a ventricular pacemaker may serve a dual purpose and in our opinion there is not much sense in trying to restore atrioventricular conduction by pacing from the right atrium or the coronary sinus Besides correcting bradycardia pharmacological control of tachyarrhythmias is facilitated through the protection of a pacemaker

Administration of atropine and long term monitoring are the best diagnostic aids in our hands Administration of isoprenaline or exercise tests

gave an unpredictable response Measurement of SART has no clinical significance for in our group there were patients with sinus arrest of many sec onds while their SART was barely prolonged

Etiology The sick sinus syndrome is the common denominator for a variety of disorders affecting impulse formation and conduction Although half of our patients had manifest coronary artery disease its relation to their sick sinus syndrome remains speculative In 9 patients with angiographically demonstrated marked narrowing of the sinus node artery or proximal obstruction of this artery evidence of a sick sinus syndrome or a prolonged SART was lacking while 5 of 6 patients with the clinical syndrome had no angiographical involvement of their sinus node artery Thus both diseases may be co-existent and independent (8)

Pathology Only a few morphological studies have been performed in patients with a known sick sinus syndrome (13 14 22 23 24 28) The results are still inconclusive with regard to the pathogenesis It has repeatedly been demonstrated that the sinus node in these patients will show a marked fibrosis However studies of normal ageing of the sinus node have demonstrated similar alterations (6 12 15) It remains questionable therefore whether the changes in the sinus node itself underlie the electrophysiologic abnormalities Instead additional pathology in the atrial myocardium could be of equal significance (20) So far morphological studies have shown that the atrial myocardium con the sinus node with the atrioventricular onal area always displays fibrosis or other tive changes In some instances these findings were attributed to coronary atherosclerosis but other cases were thought to be unrelated to coronary artery disease The case presented in this study also revealed an extensive scarring of the atrial myocardium which in this particular instance was thought to be caused by coronary atherosclerosis

Semantics It seems that the sick sinus node syndrome is not an entity from a morphological point of view and in fact could well be a misnomer Indeed many investigators have already argued that the disease in most patients is more likely to be caused by an exit block than by intrinsic abnormalities of the sinus node itself Until further correlative studies are performed the morphological substrate of the sick sinus node syndrome will remain a matter of dispute Until then we prefer to stick to this most common and catching label of the disorder

Although evaluation by drugs exercise and electrophysiological investigation may be helpful in establishing the diagnosis of a sick sinus syndrome a sizable number of patients will not be defined by these tests The elusive character of the sick sinus syndrome, the imprecise nature of several diagnostic procedures and the availability of effective treatment put its proper recognition and management in the hands of the suspecting clinician

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Platelet Adhesiveness in Myocardial Infarction in Relation to Clinical Course

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ABSTRACT *ADP induced and whole blood platelet* **adhesiveness have been studied by repeated measurements during the acute stage of the disease and the following two months in 86 randomly selected patients admitted to a coronary care unit because of acute central chest pain In the patients who developed ECG and enzyme changes typical of infarction (group 1), platelet adhesiveness was significantly increased on admission compared with the rest of the patients (group 2) and controls (group 3) Patients in groups 1 and 2 showed a secondary increase during the first week, but two months after admission the means had returned to values within the normal range No correlation was found between platelet adhesiveness and infarction size or fatal outcome of the disease Platelet adhesiveness did not differ between patients with ECG changes indicating a transmural infarct and those with mainly subendocardial infarction**

Considering the important role of platelets in thrombus formation (11 16) it is reasonable to assume that an enhanced platelet adhesion aggregation reaction reflects an increased risk of thromboembolism It has been shown that among patients with femoropopliteal grafts those with increased platelet adhesiveness have a significantly reduced long term patency of the arterial graft (7) An enhanced platelet adhesion aggregation reaction has also been found during the acute stage of arterial occlusions including myocardial infarction (1 2 3 18 23)

The aim of the present study was to evaluate the importance of changes in platelet reactivity in myocardial infarction by repeated measurements during the acute stage of the disease as well as during the postinfarction period and to investigate firstly at what time during the acute stage the expected increase in platelet adhesiveness might occur and secondly to what extent an abnormally high platelet adhesiveness was related to the size of the infarction and to the clinical course of the disease In some patients an attempt was also made to evaluate the possible influence of the stress situation as measured by the urinary catecholamine excretion

MATERIAL

Eighty six patients admitted to the Coronary Care Unit (CCU) at St Goran s Hospital Stockholm because of central chest pain of more than 15 min duration within 48 hours of admission were randomly selected for the study To limit the interval between onset of symptoms and the first determination of platelet reactivity the study was restricted to those in whom platelet functions could be determined within 12 hours

Of the 86 patients 61 (group 1) developed ECG and enzyme changes typical of acute myocardial infarction (AMI) (12) The ECG changes indicated a transmural infarct in 41 of the patients in group 1 in the others the infarct was judged to be mainly subendocardial No significant difference in mean age or age distribution was found between patients with transmural and subendocardial infarction Fourteen AMI patients died seven during the first week six during the second and third weeks and one patient one month after admission In three patients death was due to ventricular wall rupture in the others it was secondary to therapy resistant cardiac failure and/or severe ventricular arrhythmias Owing to technical difficulties repeated blood samples for determination of platelet adhesiveness could not be collected in one of the AMI patients who was therefore excluded from the statistical evaluation of the results

In 25 patients (group 2) the criteria for the diagnosis of AMI were not fulfilled Two patients showed signs of pulmonary embolism and were therefore not in the statistical evaluation

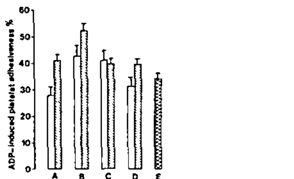


Fig 1 ADP induced platelet adhesiveness in patients admitted to the CCU due to central chest pain of more than 15 min duration A=12 hours after admission B=maximal value during the first week C=2 weeks D=2 months after admission E=patients with no history of cardiovascular disease ■=patients with AMI □=patients without AMI

All patients were observed in the CCU for at least 24 hours patients with cardiac arrhythmias A V block or other complications more than 24 hours Dicoumarol treatment was started on admission

Twenty seven patients who were admitted to the hospital during the study for surgical treatment of varicose veins inguinal hernia or gallstones but without a history of thrombophlebitis pulmonary embolism myocardial infarction or other diseases known to influence platelet adhesiveness served as a reference group (group 3)

The mean ages (±S E) in the three patient groups were as follows group 1 61 8±1 0 (range 45–78) group 2 63 0±2 0 (range 43–82) group 3 59±1 6 (range 44–74)

METHODS

Blood samples for determination of platelet adhesiveness were taken in the morning from an antecubital vein with the patient fasting The first sample (sample 1) was taken in the morning after admission to the CCU and the measurements were repeated three times during the first week of treatment (samples 2–4) and 2 weeks (sample 5) and 2 months (sample 6) after admission The blood was collected in glass tubes containing 1/10 volume of 3 13% trisodium citrate dihydrate Platelet rich plasma (PRP) was prepared by centrifuging blood at 290 g at room temperature for 15 min All glass and metal surfaces in contact with blood or plasma were siliconized

ADP induced platelet adhesiveness to glass was determined according to the method described by Hellem et al (10) The citrated PRP was passed through a glass bead column under standardized conditions immediately after the addition of ADP in a concentration of 0 10 μg/ml PRP The number of adhesive platelets was taken to be the difference between platelet counts before and after the passage expressed as a percentage of the original number

Whole blood platelet adhesiveness was measured by the method of Hellem (9) under the same conditions as described previously although without addition of ADP The error of the methods for determining ADP induced and whole blood platelet adhesiveness estimated as the S D for a single determination was 3 0 and 3 1 respectively

Platelet counts were determined with an electronic particle counter (Celloscope 202 Ljungberg Ltd Sweden) Urinary catecholamine excretion over 24 hours was determined according to von Euler and Lishajko (6) Routine 12 lead ECG including standard and precardial (CR) ECG leads were recorded with an ink jet recorder (Mingograf 61 Elema Schönander Sweden) Blood for enzyme determination of SGOT SGPT and LDH was taken on admission and at least on each of the next three mornings

RESULTS

Data on mean ADP induced platelet adhesiveness ±S E are summarized in Fig 1 The mean value measured less than 12 hours after admission was 41 0%±2 0 in patients with AMI (group 1) which was significantly higher (p<0 001) than the value of 27 9%±3 1 in patients without confirmed diagnosis of AMI (group 2) The mean on admission in group 1 was also higher than in patients with no history of thromboembolic disease (group 3) (34 0±1 9 p<0 05)

Serial determinations of ADP induced platelet adhesiveness in group 1 patients who survived the first week revealed that only a minority had their highest value on admission (Fig 2) the majority showed an increase during the first week Peak values were most frequent at the end of the first week (sample 4) The maximal value in group 1 during the first week was 52 8%±2 1 significantly higher than both the corresponding value in group 2 (p<0 02) and the mean value in group 3 (p<0 001) Two weeks after admission mean platelet adhesive

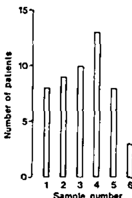


Fig 2 Peak value of ADP induced platelet adhesiveness in AMI patients in relation to sample number

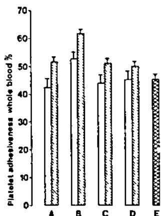


Fig 3 Whole blood platelet adhesiveness in patients admitted to the CCU due to central chest pain of more than 15 min duration Symbols as in Fig 1

ness in group 1 had fallen to 39 7%±1 9 and to 39 4%±2 2 after two months

In group 2 ADP induced platelet adhesiveness was 27 9%±3 1 on admission and increased during the first week to 42 9%±3 9 Two weeks respectively two months after admission the mean values were 41 3%±3 6 and 31 4%±3 4 (Fig 1) The difference between groups 1 and 2 was statistically different two months after admission ($p<0$ 05) The peak values during the first week and the mean value two weeks after admission were significantly higher than on admission The peak value during the first week also differed significantly from the mean in group 3 ($p<0$ 05)

Whole blood platelet adhesiveness is summarized in Fig 3 Platelet adhesiveness on admission the maximum value during the first week and the value two weeks after admission in group 1 were all significantly higher than in group 2 ($p<0$ 01 $p<0$ 001 $p<0$ 05 respectively) but no difference was found two months after admission Compared with group 3 group 1 again had significantly higher values on admission ($p<0$ 05) during the first week ($p<0$ 001) and two weeks after admission ($p<0$ 05) but not two months after admission Group 2 differed significantly ($p<0$ 02) from group 3 only with respect to the maximal value during the first week

In 14 patients who died from myocardial infarction mean maximum values of ADP induced and whole blood platelet adhesiveness were 51% (range 31–84) and 62% (range 35–91) respectively Although high values thus were found in some of the patients the mean values did not differ from those obtained in the whole group

In the 41 patients with transmural infarct neither ADP induced nor whole blood platelet adhesiveness differed significantly from the values in patients with subendocardial infarction

Maximal values of ADP induced platelet adhesiveness during the first hospital week are plotted against maximal SGOT values in Fig 4 No relation was found between either ADP induced or whole blood platelet adhesiveness and SGOT values Neither was a significant relationship found between either ADP induced or whole blood platelet adhesiveness and urinary catecholamine excretion

DISCUSSION

It has been debated to what extent an increased platelet reactivity constitutes a risk factor in myocardial infarction There are no prospective studies supporting such a concept but it has been shown that a high preoperative platelet adhesiveness is related to a reduced long term patency of the arterial graft in patients with femoropopliteal grafts (7) The present results show an increased platelet reactivity both soon after admission and during the first week in patients with myocardial infarction in accordance with earlier reports (1 2 3 18 23) The reactivity was not increased when measured within 12 hours after admission in the patients who were treated for suspected myocardial infarction but in whom the diagnosis was contradicted by a lack of ECG and serum transaminase changes This suggests that an enhanced platelet reactivity may be associated with myocardial infarction per se since both groups were treated in the same environment

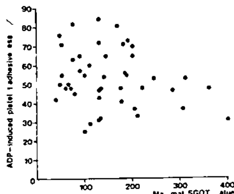


Fig 4 Maximal ADP induced platelet adhesiveness during the first week in AMI patients who survived the first week in relation to maximal SGOT value

of the CCU Although patients with myocardial in farction did differ highly significantly from non infarcted cardiac patients in platelet adhesiveness soon after admission there was some overlapping which limits the value of this parameter for the early daignosis of AMI

Patients with myocardial infarction and non infarcted cardiac patients both showed an increase in platelet reactivity during the first week of treat ment This favours the assumption that such an in crease is more of a secondary reaction than a primary event Further support for this came from the finding that both groups showed a return to initial values two months after admission Although ADP induced adhesiveness two months after ad mission was higher in the myocardial infarction than the non infarcted cardiac group the level did not differ significantly from that observed in non thrombotic patients (group 3) This result is in ac cordance with the earlier observation of a normal platelet adhesiveness in many patients with a his tory of previous myocardial infarction (21 22 23)

It might be of interest to speculate whether the in crease in platelet adhesiveness in myocardial infarc tion patients during the first week was related to the occurrence of a coronary thrombus Such a rela tion is difficult to establish since the reported in cidence of coronary thrombosis in myocardial in farction varies between autopsy materials (4 8 19 20) The variation probably reflects several factors the two most important being the type of infarction and the interval between onset of symptoms and death (4 20) The autopsy studies make it likely however that a coronary thrombosis is more com mon in patients with a transmural infarction than in those in whom the infarct is mainly subendocardial Platelet adhesiveness in these two types of infarc tion was accordingly compared but no significant difference emerged

In a recent report (5) on the incorporation of ^{125}I labelled fibrinogen into coronary arterial thrombi in myocardial infarction it was suggested that formation of the coronary thrombus could often be a secondary event The results also sug gested that the thrombus took a considerable time to develop Even if it is assumed that both the formation of a coronary thrombus and an increased platelet adhesiveness are often secondary reac tions in myocardial infarction the formation and subsequent growth of a coronary thrombus would further compromise coronary blood flow and lead to an increase in infarction size The increased platelet adhesiveness observed during the acute stage of myocardial infarction even if it is a sec ondary reaction would under these circumstances favour thrombus formation and growth and may therefore be relevant to the clinical course of the disease This assumption is supported by a recent investigation suggesting that multiple small platelet thromboemboli from an experimental coronary thrombus can enlarge a zone of regional infarction (17)

Jorgensen et al (13) have also found platelet microemboli in the microcirculation of patients dying from cardiac causes The present study how ever showed no significant relationship between peak platelet adhesiveness and maximal SGOT values the latter being taken as a rough estimate of the amount of injured myocardial tissue (14 15 24) Neither was a relation found between high levels of platelet adhesiveness and fatal outcome of the disease It is obvious that although a gener ally increased platelet reactivity may reflect an in creased risk of thrombus formation and growth other factors are more important for the onset of AMI and for the clinical course of the disease Still among a group of patients admitted to the CCU with suspected myocardial infarction those with a high platelet adhesiveness on admission and a marked increase during the first week did develop ECG and enzyme changes typical of infarction more often than the rest of the patients It is therefore still conceivable that prophylactic treatment with substances inhibiting platelet function might de crease the frequency of recurrent myocardial in farction or death from coronary heart disease

ACKNOWLEDGEMENTS

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Renal Stones and Coronary Heart Disease

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ABSTRACT The relationship between risk factors for coronary heart disease (CHD) and renal stone disease has been studied in a population of more than 2000 middle aged men The only positive association found was a slight increase in diastolic BP among stone formers and a higher stone prevalence in untreated hypertensives Furthermore the prevalence of a history of renal stones in male survivors of myocardial infarction (MI) was similar to that found in the population study An investigation of the vitamin D intake by means of a dietary questionnaire revealed no differences between stone formers, healthy controls and MI survivors Contrary to other reports, the present study indicates that the risk factor profile for CHD in stone formers is similar to that in the general population

Coronary heart disease (CHD) and renal stones are common disorders which are both believed to be increasing in frequency in the Western world Recent reports have indicated a possible association between these two diseases (10 19 20 27) The nature of such a connection is unclear but environmental factors have been postulated Some of the risk factors for CHD have also been found in unexpectedly high frequencies among renal stone formers e g high BP (26) raised serum cholesterol (27) obesity (4) impaired glucose tolerance (22) and raised serum uric acid (SUA) (6 9 23) It has previously been proposed that an overconsumption of vitamin D could be a precipitating cause for both myocardial infarction (MI) (7 16 19) and renal stones (19 25) No systematic studies have been performed to establish the nature of a possible relationship between CHD and renal stones Since the reported associations generally have been rather weak the importance of carefully selected control groups must be emphasized

This paper reports an investigation of risk factors for CHD among renal stone formers and matched controls both recruited from a population study of middle aged men The prevalence of renal stones among male MI survivors has also been analysed Finally the vitamin D intake was studied in these three groups

SUBJECTS

Between Sept 1970 and Sept 1973 a health examination was offered all men living in the City of Uppsala Sweden who were born between 1920 and 1924 (13) The aim of this investigation was to identify risk factors for CHD A total number of 2322 men were examined corresponding to a participation rate of 83 9%

A history of renal stone disease was obtained from 318 subjects (13 7%) This population has been described in detail elsewhere (20) From this material subjects with one or more of the following criteria were excluded (*a*) a probable cause for stone formation ($n=30$) (*b*) other clinical diagnosis and/or long term medication ($n=18$) Since four subjects fulfilled both criteria 274 individuals remained in the study

A matched control group was selected from the same population study The controls were apparently healthy without a history of renal stones and not on long term medication They were born in the same year and had been examined on the same day as their index person

Case history information regarding renal stone disease was also obtained from 102 consecutive male patients aged 34–70 (mean 59±8) who had survived an MI

METHODS

A self administered medical questionnaire was used at the health examination to obtain information regarding previous diseases physical activity and stress experience A history of previous MI was verified by analyses of the hospital records The information regarding smoking habits and some psychosocial data was completed by an interview The case history information regarding renal

Table I *Frequency (%) of some codable ECG abnormalities in renal stone formers and a stone free population (controls) from a health survey of 49–50 year old men*

	Code no [a]	Stone formers [b] (n=316)	Controls [c] (n=1 995)
No codable abnormality	I 0	64 6	70 4
Q items	I 1–2	0	1 6
QRS axis deviation	II 1	2 8	3 0
High QRS amplitude	III 1	11 7	8 5
S–T depression	IV 1	0	0 8
T wave items	V 1–2	3 8	2 1
A–V conduction defects	VI 1–4	2 2	2 0
Ventricular conduction defects	VII 1–2	1 9	0 9

[a] According to the Minnesota Code [b] Data missing in 2 subjects [c] Data missing in 9 subjects
[d] $p<0\ 05$ compared with controls

stones among the MI survivors was obtained through a postal questionnaire A postal questionnaire was also used to get detailed information on the intake of vitamin D from different sources natural food fortified foods and vitamin preparations The same dietary questionnaire was sent to stone formers controls and to the MI survivors The subjects were also asked about their liability to cutaneous pigmentation (classified as high or low) Drs H Lithell and B Vessby Department of Geriatrics University of Uppsala provided information on the MI survivors and dietitian I B Gustafsson the dietary questionnaire

The laboratory analyses of serum lipids SUA and blood glucose were performed by the methods used routinely at the Department of Clinical Chemistry and described elsewhere (13) The serum lipoprotein patterns were analysed in subjects with hyperlipidemia The glucose tolerance was estimated using an i v glucose tolerance test and expressed as the K value (15) The relative body weight weight index was calculated as actual over ideal weight using the tables of Lindeberg et al (17) A 12 lead resting ECG was recorded The ECGs were classified according to the Minnesota Code (3) by two experienced physicians at the Department of Clinical Physiology

Conventional statistical methods were used for calculations of mean values and S D Significances of differences between mean values were estimated by means of Student s t test (two tailed test) The χ^2 test for small populations with Yates correction was used for comparison of frequencies The accepted level of significance was $p<0\ 05$

RESULTS

ECG findings and prevalence of myocardial infarction

Fifteen participants (0 6%) in the health survey had suffered an MI before the examination Three of them reported a history of renal stones The prevalence of MI in stone formers was not different from that in the stone free population In the series of 102 consecutive male MI survivors the prevalence of renal stones was 12 8% which was not significantly different from the frequency of 13 7% obtained in the health survey

Some ECG findings among the total number of stone formers and the remaining entire population are listed in Table I ECGs without codable abnormalities were less common in stone formers but there was no difference for any of the specific pathological items

Clinical and laboratory variables

Some clinical and laboratory data on the 274 renal stone formers and their matched controls are presented in Table II The average diastolic BP (DBP) but not the systolic was slightly raised in the stone formers The raised mean value for DBP was due to a greater number of individuals in the highest ranges thus 7 4% of the stone formers had a DBP≥105 mmHg compared with 2 0% among the controls ($p<0\ 05$) Furthermore among 86 subjects in the total population with an untreated DBP≥105 mmHg 17 men (19 8%) had a history of renal stone

Table II *Systolic (SBP) and diastolic (DBP) blood pressure weight index glucose tolerance (K value) and serum uric acid (SUA) in 274 renal stone formers and matched controls from a health examination survey of 49–50 year old men (mean±S D)*

	Stone formers	Controls
SBP (mmHg)	133 7 ±19 1	131 4 ±14 9
DBP (mmHg)	84 7 ±11 5	82 5 ± 9 7
Weight index	1 09± 0 15	1 09± 0 13
K value	1 78± 0 70	1 68± 0 69
SUA (mg/100 ml)	4 27± 0 93	4 30± 0 93

* $p<0\ 05$ compared with controls

Table III *Serum lipid concentrations (mean ±S D) and frequencies (%) of hyperlipoproteinemias (HLP) in 274 renal stone formers and matched controls from a health survey of 49–50 year-old men*

	Stone formers	Controls
Cholesterol (mg/100 ml)	235±43	233±39
Triglycerides (mmol/l)	1 75±1 00	1 79±1 11
Type of HLP[a]		
IIA	5 1	5 1
IIB	2 6	3 6
III	1 1	1 1
IV	3 3	5 1

[a] Classified according to the recommendations by Beaumont et al (2)

disease This was significantly more than in the normotensive (DBP<105 mmHg) population ($p<0\ 05$) The prevalence of renal stones was 12 9% among 85 subjects with treated hypertension and 14 1% among those with the lowest DBPs (≤70 mmHg) These frequencies were not different from that in the total population Stone formers and their controls had exactly the same weight index The mean values for SUA were also almost identical Diabetes mellitus was present in the same frequency (0 6%) among stone formers and controls Nor were there any differences in glucose tolerance between the two groups

Mean values for serum cholesterol and triglycerides and the frequencies of different types of hyperlipoproteinemia (HLP) did not differ between stone formers and their matched controls (Table III) Furthermore in 261 men with HLP (14) the stone prevalence was 11 9% which was not different from that in the normolipidemic population Nor were there any differences in stone prevalence between the various types of HLP

Smoking habits physical activity and psychosocial factors

Smoking was equally common among stone formers (46 6%) and controls (44 0%) There were no detectable differences in duration of smoking number of cigarettes smokes daily or other smoking habits Stone formers more often had predominantly sedentary work than the controls 43 1% and 35 8% respectively ($p<0\ 05$) The degree of physical activity during leisure was similar in the two groups No differences concerning stress experience were found from information based on a standard questionnaire Concerning marital status 6 6% of the stone formers were unmarried which was significantly less than 15 3% among the controls ($p<0\ 01$)

Risk factors in relation to course of stone disease

Subjects with a history of renal stones were also classified according to age at onset of disease total number of stones interval since last stone passage and family history of stones All these subgroups showed similar risk factor profiles and no differences appeared in any of the variables above

Vitamin D intake liability to cutaneous pigmentation

The daily intake of vitamin D for stone formers controls and MI survivors is shown in Table IV None of the differences between the groups are significant nor were the differences in liability to develop cutaneous pigmentation Vitamin D was almost entirely ingested from natural and fortified foods since less than 5% of the individuals reported regular use of commercial preparations containing vitamin D

DISCUSSION

In the present study of middle aged men the only significant relationships between risk factors for CHD and renal stone formation were a slight elevation of DBP in stone formers and a higher frequency of renal stones in untreated hypertensives This finding is in accordance with an earlier report by Tibblin (26) However although the small numerical increase in DBP was statistically significant this

Table IV *Daily consumption of vitamin D and liability to develop cutaneous pigmentation among 60 renal stone formers and 100 controls from a health survey of 49–50-year-old men and in 102 male MI patients (mean±S D)*

	Vitamin D consumption (μg/day)	Liability to pigmentation (%) High	Liability to pigmentation (%) Low
Stone formers	8 10±7 65	91 7	8 3
Controls	9 75±6 75	85 0	15 0
MI patients	9 25±5 00	85 3	14 7

could not be expected to be of particular im portance for the predisposition to CHD

A sedentary occupation was more common among stone formers than among controls This is of interest since this form of work is becoming more widespread in the Western world where stone incidence is likewise reported to be increasing (1) The sedentary life style has also been implicated as a coronary risk factor (24)

The lack of correlation found in this study be tween other CHD risk factors and renal stones is not consistent with some previous reports (4 6 9 22 23 27) Generally these studies have reported slight increases for various risk factors in stone formers although not primarily concerned with these variables in relation to CHD However all these parameters are known to vary considerably with for example age sex body weight and sea son In our study the controls were of the same age and sex and were also matched for time of investi gation The discrepancy between the present study and some of the others may to some extent be due to different methods of selection of control materi als Most other studies have dealt with patients with recurrent stones In the present population study there were no differences in the risk factor pattern between subjects with multiple or single stones This enabled us to consider all stone formers to gether and thus does not explain the differences compared with investigations of patients selected from stone clinics

It should be emphasized that the stone formers were not more overweight than the control sub jects This is of particular importance since even moderate obesity has been shown to be associated with disturbances in the metabolism of glucose lipids lipoproteins (5) and uric acid (21)

Geographic variations due to both genetic and local environmental factors could also be of im portance Such factors are well known for CHD but there is no reliable information regarding stone dis ease in the population Furthermore a previous report from the same population study indicated that the epidemiology of renal stones could not be evaluated from hospital statistics (20) Among the factors responsible for geographic variations in the prevalence of CHD different dietary habits have been discussed (24) In a recent study from Nor way interest was focused on the intake of vitamin D (19) A significant association was found between CHD and renal stones both disorders being related to a high consumption of commercial vitamin D preparations

A causal relationship between an excessive in take of vitamin D and renal stones does not seem unlikely (25) Vitamin D might also be harmful to the cardiovascular system perhaps through a dis turbed cholesterol metabolism (7 16) These rela tionships are probably dose dependent In our study the daily consumption of vitamin D both in patients and controls was below 10 μg This figure compares favourably with other estimates of vita min D intake in the general population (8 12) In the Norwegian study cited above daily vitamin D con sumption was 2–3 times higher in the various groups Although dietary questionnaires certainly do not give exact information (11) these large dif ferences probably reflect true variations in dietary habits The association found in some other studies between CHD and renal stones could thus perhaps be explained by a high vitamin D intake in both groups

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Maximal Bioavailability of Digoxin from Tablets and Oral Solution in Steady State

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ABSTRACT Comparison has been made between the absorption of digoxin from Lanoxin® tablets and the absorption of international chemical reference substance digoxin from an oral solution Plasma levels, areas under 24-hour plasma concentration curves and urinary excretion were similar by both formulations In steady state 78% of the digoxin administered was absorbed from the tablets and 76% from the solution Rapid dissolution in the intestinal fluids accounts for the high digoxin bioavailability of the tablets

Digoxin has proved to be a highly problematical drug for the pharmaceutical industry the medical authorities and the physicians prescribing it Differences in uniformity of content and bioavailability of digoxin tablets are well established (11 15) Medical authorities have advised physicians to avoid a number of tablet brands of digoxin (7) Due to the critical nature of digoxin in therapy suitable methods for standardization and improvement of the quality of digoxin tablets are sought High bioavailability of digoxin is associated with rapid dissolution of the tablets (2 8 12 19) However the maximal absorption of digoxin from tablets has not been fully elucidated To test whether further improvement in bioavailability might be possible the absorption has been compared in steady state conditions from rapid dissolution tablets and from oral digoxin solution

VOLUNTEERS AND METHODS

Eleven healthy volunteers (age 18–49 years weight 47–73 kg) underwent two consecutive 10-day treatment periods in a random cross over manner All had normal serum creatinine levels They ingested 0 25 mg digoxin with 100 ml water after a night s fasting Eating was allowed 2 hours later and the subjects continued with their normal diets

Blood samples were obtained immediately before the ingestion of the daily digoxin dose between days 8 and 10 Further blood samples were taken on day 10 at ½ 1 2 4 8 and 24 hours after ingestion of digoxin The 24-hour sample was also used as the 11th day value when calculating the mean steady state plasma digoxin level Urine was collected on days 9 and 10 during both treatment periods

The Lanoxin® brand of digoxin was used (Burroughs Wellcome lot 3371S) and the tablets were found to comply in all respects with the requirements of the BP 1973 for digoxin tablets and with the USP XVIII 6th interim revision announcement of tablet dissolution The percentage dissolution (±S D) was 91 0±3 0 95 6±3 6 and 98 6±2 4 at 15 30 and 60 min respectively

Doses of standard digoxin solution were prepared from the Int Chem Ref Subst Digoxin as follows digoxin 0 00025 g propylene glycol 0 4 g ethanol 0 1 g and water ad 10 ml Each dose (10 ml) was enclosed in a vial and sealed with a rubber plug

Plasma was quickly separated from the blood samples and stored frozen at −20°C Aliquots of urine were stored similarly All samples from a single subject were measured in the same series Digoxin was determined in duplicate by radioimmunoassay using Lanoxitest β reagent kits (16) The coefficient of variation was 3 6% and the recovery from urine was 98%

Standard statistical methods for paired observations were applied in calculations of statistical significances

RESULTS

When measured from the 8–11 day samples the mean (±S E) steady state plasma level of digoxin was 0 464±0 039 ng/ml during the period of digoxin solution and 0 480±0 035 ng/ml during the tablets The difference between these two means is not significant (t=0 245) When digoxin solution was given the mean individual concentrations varied from 0 32 to 0 66 ng/ml and during the tablet period

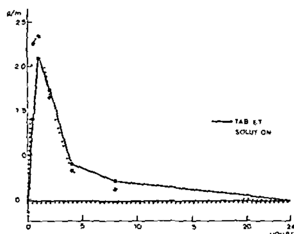


Fig 1 Mean plasma digoxin concentration in 11 healthy volunteers in steady state after ingestion of 0 25 mg digoxin either from tablets or oral solution

from 0 31 to 0 70 ng/ml Three subjects had higher concentrations during the solution period and 3 others during the tablets while in the remaining 5 subjects no obvious differences were seen

As shown in Fig 1 ingestion of 0 25 mg digoxin from solution produced slightly higher and more rapid peak plasma concentrations than that from the tablets However no significant differences (t= 0 835) could be detected in the areas under 24 hour plasma concentration curves when the steady state levels were used as baseline The calculated area (±S E) was 6 89±0 63 and 7 27±0 47 ng/ml × h for the solution and the tablets respectively

The mean (±S E) 24 hour urinary excretion of digoxin on days 9 and 10 was 146 4±5 60 μg during the solution and 150 5±6 03 μg during the tablet period This difference was also insignificant (t= 0 638) Urinary excretion varied between 117 and 169 μg with the solution and between 124 and 182 μg with the tablets The mean urinary excretion was 58 5% of the daily digoxin dose with the solution and 60 3% with the tablets

DISCUSSION

Differences in digoxin bioavailability between various tablets are well established There is however a striking lack of uniformity in the determinations of bioavailability and reference standards between various investigators making it often difficult to interpret results accurately Differences in bioavailability of digoxin are related to variations in the rate of digoxin release from the tablets (2 8 12 19) and to variations in digoxin particle size (10 20) Oral solution provides digoxin available immediately for intestinal absorption By using this as a standard for bioavailability comparisons are focused on the ability of the tablets to release digoxin in intestinal fluids

In the present study the bioavailability of digoxin from tablets was compared in steady state with that from an oral solution of international chemical reference digoxin in 11 healthy volunteers No differences could be detected in plasma steady state digoxin concentrations in areas under 24 hour absorption curves or in urinary excretion of digoxin showing that similar absorption was indicated from tablets and oral solution by three different measures of absorption The absorption rate was slightly higher from the solution than from the tablets although the dissolution rate of the tablets was rapid enough to ensure a total absorption similar to that of the oral solution

In steady state urinary recoveries were 60 3% and 58 5% of the daily digoxin dose with the tablets and the solution respectively Calculated on the basis of 76–80% urinary recovery of i v injected digoxin (1 3) it yields 78% and 76% total absorption respectively for the tablets and the solution which is in close agreement with results from investigations of other oral liquid digoxin preparations (1 3 9)

Inconsistent results have been reported from comparisons between digoxin absorption from tablets and from oral solutions (3 4 5 9) Most investigators have applied single dose experiments in comparisons of bioavailability However maintenance studies in steady state offer the most reliable estimate of clinical digoxin bioavailability (18) Huffman et al (5) found lower bioavailability of digoxin from Lanoxin tablets made in the USA than from an oral solution and although this may have been due to differences between Lanoxin tablets made in the UK and USA it is more probably a result of the postprandial administration of the drug in this study It is known that food especially a fatty meal can diminish digoxin bioavailability (Reissell to be published) Absorption from tablets is likely to be more vulnerable than that from solution

Johnson and Lader (9) suggested that certain solvents might improve the bioavailability of digoxin The clinical significance of this solvent facilitated improvement in absorption is doubtful in the

light of great variations in individual capacities for digoxin absorption which shows that digoxin is almost never totally absorbed Even in the better absorbed digoxin derivative β methyl digoxin large variations in individual absorption capacities are suggested (6)

The present results with Lanoxin tablets show that the same degree of absorption can be achieved by tablets as by oral solutions making it unnecessary to introduce digoxin liquid capsules or other less convenient formulations for routine use If the rate of dissolution is a dominant factor in absorption (2 8 12 19) the present results hold for all tablet brands of rapid dissolution It seems likely that the pharmaceutical industry will succeed in assessing the problem of the varying bioavailability of different digoxin tablets However the difficulties due to variations in individual capacities for digoxin absorption excretion and sensitivity remain

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Effects of Metoprolol in Angina Pectoris

A Subacute Study with Exercise Tests and a Long term Tolerability Study

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ABSTRACT Eighteen patients with angina pectoris who had previously participated in a cross over study with 20 mg metoprolol t i d and placebo have been included in this study During an introductory six month open tolerability study, all patients were treated with 50 mg metoprolol t i d and during a subsequent cross-over study the efficacy of this dose was compared with that of placebo under double blind conditions An exercise test was performed at the end of each cross-over period Metoprolol in a dose of 50 mg t i d gave a significant improvement compared with placebo in respect of the number of anginal attacks, nitroglycerin consumption and daily subjective assessment of the patients anginal symptoms Metoprolol also gave a significant increase in exercise capacity, both until the appearance of 1 mm ST segment depression and until the end of exercise Heart rate and blood pressure were reduced both at rest and during exercise No severe unwanted effects were observed during this study ranging over eight months and none of the patients had any signs or symptoms of cardiac failure or pulmonary dysfunction on any occasion Unwanted effects reported were mild to moderate and the frequency was the same as during placebo treatment No abnormal laboratory findings were observed and the relative heart volume was not significantly changed Administration of 50 mg metoprolol t i d seems to be of greater benefit than 20 mg metoprolol t i d , previously investigated in these patients

In a previous study (8) a rather low dose 20 mg t i d of metoprolol (Metoprolol (pINN)=H 93/26 Seloken® Hassle Sweden and CGP 2175 CIBA GEIGY Switzerland) was evaluated in comparison with placebo in patients with angina pectoris However as that dose of metoprolol turned out to be too low to produce any marked reduction (≥10%) in exercise induced tachycardia in about 30% of the patients it was decided to evaluate 50 mg metoprolol t i d in order to determine whether this dose had a more pronounced effect on the anginal symptoms than 20 mg t i d in the patients who had participated in the previous investigation

MATERIAL

Eighteen patients with typical angina pectoris according to a questionnaire modified after Rose (10) were included in this study All had previously participated in a cross-over study with 20 mg metoprolol t i d and placebo without any severe unwanted effects or signs or symptoms of cardiac failure Pertinent clinical information is given in Table I Before entering the study all patients were informed about the aims and procedures of the study and all consented to participate

METHODS

Design of the study (Fig 1)

During an introductory open *long term tolerability study (LTTS)* over six months the patients were treated with 50 mg metoprolol t i d The purpose of this part of the study was to accumulate data regarding tolerance of the drug

The LTTS was followed by a *cross over study* with two double blind periods of four weeks each During these periods the patients were given 50 mg metoprolol t i d or placebo in randomized order

At control visits (Fig 1) physical examination was performed and *unwanted effects* were registered according to a standardized questionnaire and the following *laboratory tests were performed Hb WBC thrombocytes* serum creatinine bilirubin alkaline phosphatase SGOT and SGPT *Exercise tests* were performed at the

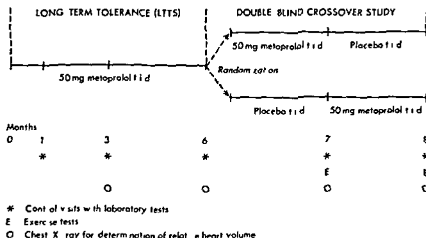


Fig 1 Design of the study

end of each cross-over period The *relative heart volume* (RHV) was determined after 3 and 6 months and at the end of each cross-over period

Clinical assessments

During the cross-over study the patients were instructed to complete a simple diary card This card showed the daily number of anginal attacks the number of nitroglycerin tablets taken each day and a daily subjective assessment of symptoms of angina pectoris according to a four point scale Each day was rated as more severe as usual milder or symptom free

Exercise tests were performed about 1 5 hours after the last tablet intake The tests were performed with 30-watt increases in the work load every 6 min starting at 30 W The exercise was stopped when the patient suffered the same degree of anginal pain as would have forced him to stop his activity in everyday life Heart rate and systolic BP were registered after 4–6 min at each work load at the end of work and 2 and 6 min after ceasing work Total work exercise capacity until onset of pain and until 1 mm of ST depression were calculated as the sum of the product of work load and working time on each work load

The tablets used in the LTTS and the cross over study were identical in appearance and taste

Statistical methods

Wilcoxon s matched pairs signed ranks test was used for intrapatient comparison of non parametric data and Student s t test for comparison of parametric data The χ^2 test was used for testing the significance of subjectively reported changes and the Spearman rank test for correlations (13) All p values refer to two tailed tests

Table I *Clinical information*

No of patients	18
Males	14
Females	4
Age (y)	
Mean	51
Range	39–65
Duration of angina pectoris (y)	
Mean	5
Range	1–17
No of patients with a history of previous myocardial infarction	8
No of patients with other diagnoses	
Intermittent claudication	1
Hyperlipemia	7
Diabetes mellitus	2
Cardiac failure	2
Hypertension	2
Aortic coarctation	1

RESULTS

Eighteen patients entered this study and 16 completed it as planned One patient (no 3) moved to another area and was never included in the cross-over study Another patient (no 5) was withdrawn from the study during the second cross over period with metoprolol due to a viral meningitis Neither of these drop outs was related to the metoprolol therapy

Clinical assessments in the cross over study

Number of anginal attacks Compared with placebo the investigated dose 50 mg metoprolol t i d gave a significant reduction in the number of anginal attacks per week ($p<0.01$) The average reduction was about 30% In seven patients the reduction after metoprolol was >20% and none of the patients deteriorated on metoprolol compared with placebo One patient (no 18) had not completed his diary card satisfactorily and could not be evaluated with regard to this parameter (Table II)

Nitroglycerin consumption Also with regard to

Table II *Effects of 50 mg metoprolol t i d and placebo on attacks per week and nitroglycerin consumption per week in 15 patients*

	Median	Range	p value
Attacks per week			
Metoprolol	6	3–70	
Placebo	9	7–125	<0 01
Nitroglycerin tablets per week			
Metoprolol	3	1–30	
Placebo	5	2–38	<0 01

this parameter a significant reduction was obtained after metoprolol compared with placebo ($p<0\ 01$) The average reduction was 40% (Table II) >20% in ten patients None of the patients deteriorated on metoprolol compared with placebo

Subjective daily assessment of symptoms of angina pectoris The daily rating of symptoms of angina pectoris showed a significant improvement after metoprolol compared with placebo with a marked reduction in the number of severe days and an increase in the number of milder and symptom free days ($p<0\ 001$) (Fig 2)

Exercise tests in the cross over study

Exercise tolerance Mean values for the variables recorded during exercise are given in Table III

Total work was significantly increased after metoprolol compared with placebo the difference averaging 16% ($p<0\ 01$) Four patients increased

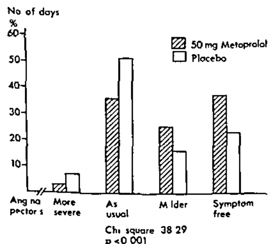


Fig 2 Subjective daily assessments of anginal symptoms

Table III *Effects of 50 mg metoprolol t i d on exercise test*

	Mean	Median	S E M	p values
Total work until 1 mm ST depression (W min) (n=12)				
Metoprolol	533	450	101	
Placebo	385	300	65	<0 05
Total work until onset of pain (W min) (n=15)				
Metoprolol	567	630	102	
Placebo	514	480	101	N S
Total work at end of exercise (W min) (n=16)				
Metoprolol	842	743	104	
Placebo	724	608	120	<0 01
Heart rate at rest (beats/min) (n 16)				
Metoprolol	60		1 7	
Placebo	73		2 5	<0 001
Heart rate at 6 at 30 W (beats/min) (n=15)				
Metoprolol	73		2 8	
Placebo	92		4 2	<0 001
Arterial systolic/diastolic BP at rest (mmHg) (n=16)				
Metoprolol	141/88		4 0/2 6	
Placebo	148/94		4 6/2 2	<0 05/<0 02
Systolic BP at 6 at 30 W (mmHg) (n=15)				
Metoprolol	159		6 6	
Placebo	166		4 9	N S
Rate pressure product at 6 at 30 W×10 ² (n=15)				
Metoprolol	115		4 9	
Placebo	154		9 3	<0 001

their total work by more than 50% and six by more than 20% In five cases the difference was less than ±20% and in one case placebo was the better drug

Total work until *onset of pain* was not significantly increased after metoprolol compared with placebo Eight patients increased their exercise capacity by more than 20% compared with placebo In five cases there was a difference of less than ±20% between metoprolol and placebo and in two cases placebo was the better drug One patient (no 17) did not experience the same degree of anginal pain on metoprolol as on placebo and stopped mainly due to fatigue

ECG reaction The mean increase in exercise capacity until the appearance of 1 mm ST segment depression was 38% after metoprolol compared with placebo Six patients increased their capacity by more than 50% In five cases the difference between metoprolol and placebo was less than

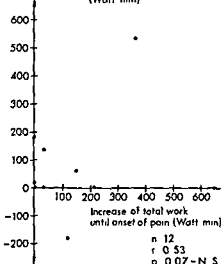


Fig 3 Increase in total work until 1 mm ST depression in relation to the increase until onset of pain after metoprolol compared with placebo

±20% and in one case placebo was the better drug Four patients had no ST depression during exercise one of them only during metoprolol treatment

Correlation between the time until appearance of pain and time until appearance of ST depression

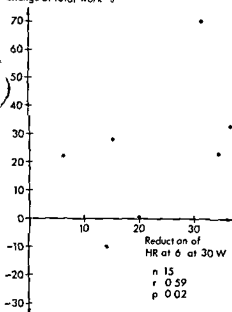


Fig 4 Percentage change in total work in relation to the reduction of the exercise tachycardia after metoprolol compared with placebo

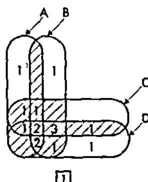


Fig 5 A modification of Venn s four set diagram indicating the distribution of responders (▨) and non responders (□) to metoprolol compared with placebo *A*=increase in total work by >20% until 1 mm ST segment depression *B*=increase in total work by >20% *C*=reduction of attack rate by >20% *D*=reduction of nitroglycerin consumption by >20% ×)=patient 18 ST depression only during placebo treatment

The exercise capacity until onset of pain and until the appearance of 1 mm ST depression was increased after metoprolol A weak correlation was found between these variables (Fig 3)

Heart rate and blood pressure Average *heart rate* was reduced by about 13 beats/min at rest ($p<0.001$) and by 19 beats/min during exercise ($p<0.001$) Two patients (nos 10 and 15) had a bradycardia with heart rates of 48 and 47 beats/min respectively but without any subjective symptoms

The *systolic and diastolic BPs* were significantly reduced at rest The systolic BP tended to decrease during exercise but the reduction was not statistically significant

Rate-pressure product The product of systolic BP and heart rate during exercise was significantly reduced after metoprolol compared with placebo ($p<0.001$) The reduction was not significantly correlated to the increase in total work

Correlation between exercise tachycardia and total work The exercise tachycardia was reduced by 23 beats/min compared with placebo A direct correlation was found between the reduction of exercise tachycardia and total work performed ($p=0.02$) (Fig 4)

Total response

An individual *total response* was estimated in order to correlate the subjective assessments of the number of anginal attacks and nitroglycerin consumption with the more objective assessments of

Table IV *Relative heart volume (ml/m² BSA)*

	Mean	S E M
Run in placebo	399	11 3
Cross-over study		
Metoprolol 20 mg	411	11 5
Placebo	408	12 5
LTTS (metoprolol 50 mg t i d)		
3 months	422	16 2
6 months	423	13 6
Cross-over study		
Metoprolol 50 mg	417	15 7
Placebo	418	15 4

total work performed until the appearance of 1 mm ST depression or until the end of exercise (Fig 5)

Postulating that patients with an improvement of at least 20% in at least two of these variables are responders 12 of the 16 patients can be regarded as *responders* to metoprolol In all except patient 7 the improvement was a combined improvement with regard to exercise capacity and subjective assessment Patient 7 showed a marked improvement after metoprolol with regard to attack rate and nitroglycerin consumption but not with regard to exercise capacity Four patients are classified as *non responders* One of them improved with regard to total work and one with regard to nitroglycerin consumption Patient 18 could be evaluated only with regard to the exercise variables because he had not completed his diary card satisfactorily This patient had no ST depression on metoprolol but did have on placebo which may be regarded as an improvement In one case no improvement at all was seen after metoprolol compared with placebo

Relative heart volume and laboratory investigations

Summarized results for RHV from the run in period in the previous study with 20 mg metoprolol t i d and the subsequent six months chronic treatment with 50 mg metoprolol t i d are given in Table IV The individual variations after six months chronic treatment with 50 mg metoprolol compared with

Table V *Severity score of unwanted effects*

1=mild (no significant interference with normal daily activity acceptable) 2=moderate (significant interference with normal daily activity but still acceptable to the patient and/or the doctor) 3=severe (unacceptable and treatment changed or stopped)

	Cross-over study						Long term tolerance study with 50 mg metoprolol t i d								
	Metoprolol			Placebo			1 month			3 months			6 months		
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
Palpitations	3			3	1		2	1		3			3	1	
Shortness of breath	5			5			2	1		4	1		5		
Heartburn	4			3			3			4	1		3		
Nausea	2			1			1	1		2			2		
Gastric pain	2			4			1	2		3			5		
Constipation	1			2			1			3			3		
Diarrhoea	2			2			3	2			2		2	1	
Flatulence	2			3	1		3	1		2	1		3	1	
Headache	4			3	2		2	1		4	1		3	1	
Insomnia	5	1		6			2			8			6	1	
Visual disturbances	2			2			1								
Tiredness	7			6	1		3	1		2	2		4	2	
Depression	1			1	1		1			2			2		
Dizziness	2			4	1		2	1		3			2		
Exanthema	1			2											
Pruritus	2			2				1		2			1		
Numbness of the fingers				1				1							
Claudication intermittent		1		1											
Muscle pain														1	
Backache					1		1								
Tremor in the right leg					1									1	
Extrasystole							1								
Numbness of the feet								1			1				
Total	45	2	0	51	9	0	29	14	0	42	9	0	44	9	0

previous run in values were less than ±100 ml in all except one patient (no 15) who decreased by 120 ml during metoprolol treatment

Metoprolol caused no abnormal variations with regard to laboratory tests performed during this long term study The individual variations in patients body weights were within ±5 kg compared with placebo in all patients except one (no 18) who gained 6 kg in weight

Unwanted effects

At each control visit the patients were questioned concerning unwanted effects according to a standardized protocol No severe unwanted effects were observed during this study ranging over six months The unwanted effects reported were mild to moderate and the frequency was about the same with metoprolol and placebo (Table V) None of the patients had any signs or symptoms of cardiac failure or pulmonary dysfunction No tachyphylaxis was observed during the LTTS

DISCUSSION

Effects of 50 mg metoprolol t i d compared with placebo on daily anginal symptoms and exercise tolerance

Although a significant reduction of both the attack rate and the nitroglycerin consumption was demonstrated after metoprolol compared with placebo these variables should be considered together when assessing the clinical benefit of an antianginal drug as a reduced attack rate might be due to an increased nitroglycerin consumption and vice versa In this study 50% of the patients were improved by >20% on both variables and 50% with regard to one variable None of the patients deteriorated on metoprolol compared with placebo with regard to either of these variables

The more objective assessments of exercise capacity have been suggested as being the most reliable variables when assessing the efficacy of antianginal drugs especially in patients with a low attack rate (6 11) As some of the patients had a rather low attack rate on placebo i e less than 5 attacks per week this might be true for this study too The increase in exercise capacity was of the same magnitude as demonstrated with 100 mg alprenolol (2 7) and 40 mg propranolol (3 5) Furthermore a weak correlation was found between the time until appearance of pain and the time until ST segment changes during exercise This correlation between the subjective symptomatic effect and the more objective one on ECG demonstrates the reliability of exercise tests when studying β blockers in angina pectoris Similar results were reported by Adolfsson et al (1) comparing alprenolol and metoprolol and by Sharma et al (12) comparing oxprenolol and propranolol

The effect of β blockers in angina pectoris is probably mainly due to a reduction of the oxygen consumption owing to a decrease in heart rate BP and contractility of the heart (1) As a reduction of the rate–pressure product has been found to correlate well to the myocardial oxygen consumption (9) it was assumed that the reduction of this product would be directly correlated to the increase in total work performed However no such correlation was found On the other hand a direct correlation was found between the increase in total work and the reduction of the heart rate at the highest comparable work load (Fig 4) Applying a 20% increase in total work as the limit for response a reduction of the exercise tachycardia by at least 15 beats/min was thus required in most cases In two cases higher doses of metoprolol might have been of further benefit

In addition to the assessments of the therapeutic effect special attention was paid to unwanted effects For these assessments a comparison with placebo gives a true picture of the net effects of the drug provided it is performed under standardized double blind conditions In the present study unwanted effects were registered according to a standardized protocol used at each control visit by the same physician No severe unwanted effects were seen and none of the patients had any signs or symptoms of cardiac failure on any occasion during this study with 50 mg metoprolol t i d ranging over seven months Mild to moderate unwanted effects were similar in frequency during metoprolol and placebo treatment

The laboratory tests performed showed no pathological variations and the RHV was not singificantly affected after metoprolol in any of these patients

Retrospective comparison between the doses of 50 and 20 mg metoprolol administered to the same patients

Another study in the same angina pectoris patients (8) was carried out one year earlier during the same

time of year (Jan–March) which should minimize climatic variations in the daily activity of the patients Although a retrospective approach has many drawbacks it is of interest to compare the effects of the two dose levels in the same patients Compared with placebo the attack rate and the nitroglycerin consumption were significantly reduced in the previous investigation with a dose of 20 mg metoprolol t i d as well as in the present study with 50 mg t i d The difference in effect between the two dose levels seemed to be negligible on these two variables

Comparison of the two dose levels with regard to exercise capacity showed that 10 of 16 patients exhibited a difference of >20% with regard to exercise capacity until 1 mm of ST segment depression and/or end of exercise According to this 20% limit seven of them can be regarded as responders to the 50 mg dose and three to the 20 mg dose These findings indicate that exercise tests probably discriminate better between different dose levels of β blockers than nitroglycerin consumption and attack rate This conclusion is in accordance with the findings of Sandler (11) and Hetherington et al (6) The lack of response to the 50 mg dose compared with the 20 mg dose found in three patients might be explained by an increased heart size as suggested by Dagenais et al (4) However in these three patients the difference between the two dose levels with regard to RHV was less than ± 30 ml/m² BSA

With regard to the hemodynamic variables a dose-dependent reduction was found for heart rate and BP as well as for the rate-pressure product The difference was most pronounced during exercise No tachyphylaxis could be detected in any of these patients when comparing the results from the two cross-over studies separated by a period of six months during which all patients were treated with 50 mg metoprolol t i d

None of the reported unwanted effects was found to be dose-dependent

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Antihypertensive Effect and Side-effects of Bendroflumethiazide and Propranolol

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ABSTRACT The antihypertensive effect and side-effects during 12 months treatment with bendroflumethiazide and propranolol have been compared in two randomly selected, equally large groups (n = 53) of previously untreated male hypertensives Systolic BP above 170 or diastolic BP above 105 mmHg on two occasions were defined as hypertension The same BP reduction was achieved in both groups During the 12 months' treatment one subject on bendroflumethiazide developed diabetes mellitus and one on propranolol developed cardiac decompensation None developed gout Contrary to what had been presumed, glucose tolerance improved during 12 months' treatment with both agents, while there were no changes in fasting blood sugar, insulin or triglyceride concentrations No changes were found in serum potassium or total body potassium during 12 months bendroflumethiazide treatment, while serum potassium increased during treatment with propranolol Uric acid increased slightly during treatment with both agents Prolongation of the follow up to 24 months did not change any of the findings regarding metabolic changes during treatment The frequency of subjective side effects decreased to the same extent during treatment with both drugs It is concluded that bendroflumethiazide and propranolol are equally useful as antihypertensive agents and that the risk of impairment of glucose metabolism and potassium balance seems to be very slight during treatment with bendroflumethiazide in mild hypertension

Diuretics and β adrenergic blocking agents are today the two groups of antihypertensive agents most widely used in Sweden Both types of drug have been shown to give a moderate dose dependent BP reduction in hypertensive subjects (9 15 18 22) β adrenergic blocking drugs are well tolerated during long term treatment (15 32) and seem to reduce the frequency of symptoms (3) Diuretic drugs have been claimed to induce diabetes mellitus or to impair glucose tolerance (6 31) to decrease serum potassium and total body potassium (10 14) and to increase serum uric acid and hence the risk for gouty arthritis (12) In Scandinavia these metabolic side effects have been regarded as a severe disadvantage in long term treatment of hypertension as they imply an insidious risk of severe side effects necessitating frequent laboratory controls However opinions have varied concerning the risk of developing these side effects and their clinical importance has been questioned by other authors (2 8 16 27) Thus there is a need for further studies to increase the possibility of assessing the therapeutic usefulness of drugs in the long term treatment of hypertensive patients

The present study is a comparison of the antihypertensive effect and side effects of a diuretic bendroflumethiazide and a β-adrenergic blocking drug propranolol The aim was to determine the antihypertensive effect and side effects of the two drugs with special regard to the metabolic side effects of bendroflumethiazide A second objective was to try to characterize those subjects who developed metabolic side effects during bendroflumethiazide treatment

PATIENTS AND METHODS

Hypertensive subjects were recruited from a primary preventive trial against myocardial infarction and stroke (29) One hundred and twenty nine men born between 1915 and 1925 with BPs at a screening examination and a subsequent check up above 170 mmHg systolic or 105 diastolic participated in the study All subjects were previously untreated Sixty four subjects were randomly allocated to bendroflumethiazide and 65 to propranolol treatment One subject allocated to bendroflumethiazide never entered the trial owing to very high BPs at screening and check up (Single-drug treatment was not regarded as a suitable antihypertensive regimen for this patient) Eight hypertensives six allocated to bendroflumethiazide and

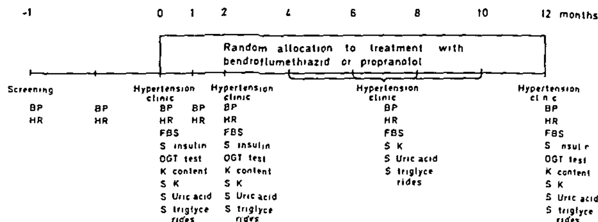


Fig 1 Design of the study

two to propranolol treatment were not included in the trial owing to BPs below 160 mmHg systolic and 95 diastolic at the first visit to the Hypertension Clinic (Fig 1) Thus 57 patients started on bendroflumethiazide and 63 on propranolol treatment

During the first year after institution of therapy four patients on bendroflumethiazide were withdrawn from the trial one developed an overt diabetes mellitus and three moved from the town or refused to participate During the same period ten subjects on propranolol treatment were withdrawn from the trial two because of poor BP control (above 170 systolic or 110 mmHg diastolic at two subsequent measurements) one due to development of cardiac decompensation one owing to exacerbation of previously known intermittent claudication three because of excessive tiredness one owing to recurrence of atrial fibrillation and two because of refusal to participate Thus 53 hypertensives on each drug completed the trial They were 47-54 years of age (mean 50 8) All had benign essential hypertension as judged by a negative standardized investigation including isotope renograms (28)

The design of the study is shown in Fig 1 All participants had three BP measurements before treatment started Treatment commenced with 2 5 mg bendroflumethiazide once daily or 80 mg propranolol twice daily Commercially available brands—Salures K (2 5 mg bendroflumethiazide+0 57 g potassium chloride) and Inderal® (80 mg propranolol)—were used The dose was doubled to 5 mg bendroflumethiazide daily and 160 mg propranolol twice daily if after 2 months treatment the BP was above 160 systolic or 95 mmHg diastolic If the BP was not reduced below these limits by this dose increment no further increment was made but patients with BPs above 170 systolic or 110 mmHg diastolic at two subsequent measurements were excluded from the study

The BP at screening and at check up after 2 weeks was measured in the seated position after about 5 min rest The third measurement (at the Hypertension Clinic) was recorded in the supine position after 5 min supine rest The heart rate was recorded by ECG or pulse palpation in the supine position at the screening examination and at the subsequent check-up and in the standing position at the Hypertension Clinic A 12.5 cm broad and 26 cm long rubber cuff connected to a mercury manometer was used when measuring the BPs The diastolic BP phase 5 i e when the sound disappears was used Height and weight were measured according to Rose and Blackburn (23) The relative body weight was calculated as weight/(height−100)

An oral glucose tolerance test (OGTT) was performed at 8 a m after 12 hours fasting Venous blood samples were drawn for fasting blood sugar and insulin determinations Thereafter 100 g glucose was given orally The blood sugar concentration was again determined after 60 min The subjects were kept in the recumbent position throughout the test The blood sugar concentration was determined in whole blood by means of a glucose oxidase method using a commercially available reagent (Glox® Kabi Stockholm) and with glycerin buffered perchloric acid as protein precipitating agent (17) The blood sampling and the determination of the blood glucose concentration were performed in all instances by the same assistants The serum insulin concentration was determined by a double antibody method using a commercial radioimmunoassay kit (Phadebas Pharmacia Uppsala)

The total body potassium content was determined in a randomly selected half of the material using a whole body counter (26) Body fat was calculated as

$$\text{body weight} - \frac{\text{total body potassium content}}{68\ 1} \quad (11)$$

The serum potassium concentration was determined by a Technicon AutoAnalyzer and serum uric acid by an enzymatic method (21) Serum triglycerides were determined after an overnight fast according to a method described by Carlson (7)

Side effects were recorded with a self administered questionnaire including 21 questions regarding symptoms possibly caused by treatment with the two drugs

Means S D and correlation coefficients were calculated according to standard methods Differences in means between two groups were evaluated with a non parametric test (Mann Whitney 25) The Wilcoxon test for paired observations (25) was used for assessing differences within a group at various points of time Differences in proportion were tested with the χ^2 test Differences

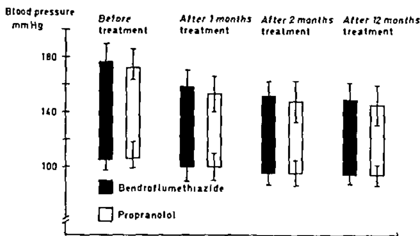


Fig 2 Blood pressure before treatment and after 1 2 and 12 months treatment with bendroflumethiazide or propranolol

were regarded as statistically significant for $p<0.05$ except for the Wilcoxon test for paired observations where $p<0.01$ was required Only two-sided tests were used

RESULTS

Blood pressure and heart rate

A statistically significant fall was noted in systolic and diastolic BPs both in the bendroflumethiazide and in the propranolol group between the screening examination and the check up after two weeks as well as between the check up and the first visit to the Hypertension Clinic (Table I) Heart rate increased significantly in both groups between the screening examination and the check up after 2 weeks and it increased further between the check up and the first visit to the Hypertension Clinic

Both systolic and diastolic BP decreased significantly during the first month s treatment with bendroflumethiazide or propranolol (Fig 2) The major part of the total BP reduction had already been achieved after 1 month s treatment Both drugs gave a slight but statistically significant fall in both systolic and diastolic BP between the measurements after 1 and 2 months but not between 2 and 12 months There was no significant difference in BP reduction between the two drugs

Thirty-one subjects completed the study on the low bendroflumethiazide dose while 22 were given the higher dose The corresponding figures for the low and high doses of propranolol were 36 and 17 patients

Heart rate did not change significantly during bendroflumethiazide treatment but fell significantly from 86 before treatment to 67 after one month s treatment with propranolol and then remained on that level for the rest of the study

Table I *Blood pressure and heart rate at the screening examination at the check up after 2 weeks and at the first visit to the Hypertension Clinic 2 weeks later for the hypertensives treated later with bendroflumethiazide or propranolol*

Treated later with	At screening x	s_x	At check up after 2 weeks x	s_x	At 1st visit to Hypertension Clinic x	s_x
Bendroflumethiazide (n=53)						
Systolic BP	183	10 3	177	10 3	176	13 6
Diastolic BP	113	8 8	110	7 6	105	7 6
Heart rate	77	11 1	85	8 0	93	15 1
Propranolol (n=53)						
Systolic BP	180	14 6	178	11 3	172	13 6
Diastolic BP	115	10 5	110	6 9	106	6 8
Heart rate	80	14 1	85	9 8	94	17 1

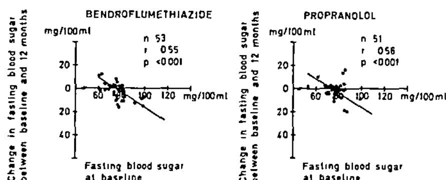


Fig 3 Relationship between fasting blood sugar at baseline and change in fasting blood sugar between baseline and 12 months treatment with bendroflumethiazide or propranolol

Glucose metabolism

There was a tendency although not statistically significant towards higher fasting blood sugar after 2 months treatment with both drugs but after 12 months treatment the fasting blood sugar concentration had returned to pretreatment values (Table II) The mean fasting blood sugar after 4 6 8 and 10 months treatment was also calculated separately for the two groups No significant differences were found between the two groups or within the groups between the various occasions of measurement

Blood glucose one hour after glucose loading decreased significantly from 172 before treatment to 149 mg/100 ml after 12 months propranolol treatment and from 171 to 158 mg/100 ml after 12 months bendroflumethiazide treatment In the propranolol group the fall in blood glucose 1 hour after glucose loading was significant after 2 months There was no significant difference between the two groups in blood glucose 1 hour after glucose loading

Plasma insulin was significantly lower after 2 months treatment with propranolol but increased again to pretreatment values after 12 months treatment In the bendroflumethiazide group plasma insulin changed in a similar manner with treatment and the increase between 2 and 12 months was significant There were no significant differences in plasma insulin between the measurements before and during treatment in either group

Table II *Fasting blood sugar concentration blood sugar concentration 1 hour after oral glucose tolerance test (OGTT) fasting plasma insulin concentration and plasma triglyceride concentration before treatment and after 2 and 12 months treatment with bendroflumethiazide or propranolol*

	Bendroflumethiazide ($n=53$)		Propranolol ($n=53$)	
	$\bar{x}$	$s_{\bar{x}}$	$\bar{x}$	$s_{\bar{x}}$
Fasting blood sugar (mg/100 ml)				
Before treatment	80	12 4	80	10 6
After 2 mo treatment	87	20 9	86	20 2
After 12 mo treatment	77	12 3	77	10 6
Blood sugar 1 h after OGTT (mg/100 ml)				
Before treatment	171	40 8	172	45 4
After 2 mo treatment	169	47 7	154	48 4
After 12 mo treatment	158	45 4	149	39 6
Plasma insulin (μU/ml)				
Before treatment	12 1	6 3	11 9	5 6
After 2 mo treatment	10 0	4 7	8 6	5 0
After 12 mo treatment	13 5	5 6	12 7	7 1
Triglycerides (mmol/l)				
Before treatment	1 6	0 7	1 6	0 7
After 2 mo treatment	1 6	0 7	1 6	0 7
After 12 mo treatment	1 6	0 7	2 0	0 9

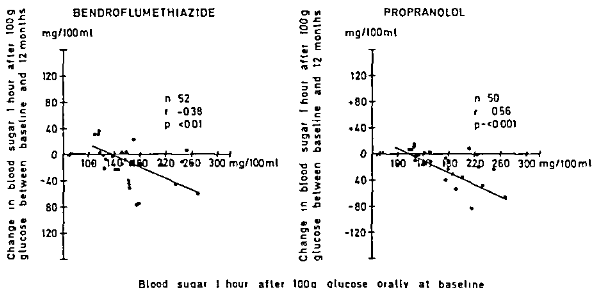


Fig 4 Relationship between blood sugar 60 after glucose loading at baseline and change in blood sugar 60 after glucose loading between baseline and 12 months treat ment with bendroflumethiazide or propranolol

No significant differences in plasma triglycerides were found during treatment in either group and there were no differences between the two groups

Potassium balance and uric acid

There were no significant changes in serum potas sium or total body potassium content during bendroflumethiazide treatment (Table III) Only one patient had a serum potassium level below 3 6 mEq/l during bendroflumethiazide treatment During propranolol treatment serum potassium in creased significantly during the first 2 months and remained at that level during the rest of the study as was confirmed by the calculated mean serum potassium after 4 6 8 10 and 12 months on pro- pranolol treatment

No patient developed gout Serum uric acid in creased slightly but significantly during the first 2 months treatment with bendroflumethiazide as well

Table III *Serum potassium total body potassium content and serum uric acid before treatment and after 2 and 12 months treatment with bendroflumethiazide or propranolol*

	Bendroflumethiazide (n=53)		Propranolol (n=53)	
	x	s_x	x	s_x
Serum potassium (mEq/l)				
Before treatment	4 2	0 3	4 1	0 3
After 2 mo treatment	4 2	0 6	4 5	0 4
After 12 mo treatment	4 2	0 5	4 5	0 4
Totabl body potassium (g)				
Before treatment	152	15 4	153[b]	16 9
After 2 mo treatment	150[a]	19 0	151[b]	15 2
After 12 mo treatment	150[a]	15 8	149[b]	17 0
Serum uric acid (mEq/l)				
Before treatment	5 1	0 9	4 9	1 1
After 2 mo treatment	5 8	1 2	5 5	1 2
After 12 mo treatment	5 7	1 3	5 4	1 3

[a] n=28 [b] n=27

Table IV *Symptoms before treatment and after 2 and 12 months of treatment with bendroflumethiazide or propranolol*

According to a questionnaire with 21 questions Before treatment one question was not put which explains the discrepancy in number

	Bendroflumethiazide		Propranolol	
	n	%	*n*	%
Before treatment	113/1 060	10 7	107/1 060	10 1
After 2 mo treatment	61/1 113	5 5	85/1 113	7 6
After 12 mo treatment	21/1 113	1 9	24/1 113	2 2

as with propranolol and remained at a higher level throughout the study as confirmed by the mean uric acid value after 4 6 10 and 12 months No significant differences in serum potassium serum uric acid or total body potassium were found between the two treatment groups at the various times of determination

Changes in glucose metabolism, potassium content and serum potassium and their relationship to pretreatment characteristics

The change in fasting blood sugar concentration between the baseline value (before treatment) and after 12 months treatment was negatively corre ..ed to the pretreatment concentration in both ..ups i e those with high initial values were those ..st apt to decrease in blood sugar (Fig 3) Furthermore the change in glucose tolerance during 12 months treatment was negatively correlated to the initial glucose tolerance (Fig 4) indicating that hypertensives with poor initial glucose tolerance were those who improved during both bendroflumethiazide and propranolol treatment

In the bendroflumethiazide group changes in the total body potassium content during 12 months of treatment were positively correlated to pretreatment body weight ($r=0\ 42$ $p<0\ 01$) body fat ($r=0\ 38$ $p<0\ 01$) and relative body weight ($r=0\ 54$ $p<0\ 001$) i e obese subjects decreased more in total body potassium content The corresponding correlation coefficients in the propranolol grup were −0 13 n s −0 23 n s −0 13 n s No correlations were found between changes in serum potassium from baseline to 12 months and baseline variables in either group

Subjective side effects

The frequency of reported symptoms before and during treatment is shown in Table IV The frequency decreased significantly between baseline and 2 months in both groups There was a further significant decrease between 2 and 12 months in both groups

Findings after 24 months treatment

All patients were followed for 24 months The results obtained at that time were mean fasting blood sugar 77±10 8 and 78±11 1 mg/100 ml blood glucose one hour after glucose loading 157±40 3 and 154±42 0 mg/100 ml, plasma insulin 12 5±4 8 and 11 5±5 2 μU/ml in the groups treated with bendroflumethiazide and propranolol respectively The mean values after 24 months did not differ significantly from those after 12 months treatment and there were no significant differences between the two groups Three patients in the bendroflumethiazide group showed increases of more than 50 mg/100 ml in blood glucose levels on loading (Fig 4) Two of them had normal values again after 24 months follow up No significant differences were found in serum potassium or serum uric acid levels between measurements made after 12 and 24 months treatment In the propranolol treated group however the uric acid level showed a tendency to decrease towards pretreatment mean value

DISCUSSION

The present subjects had mild to moderate hypertension suitable for treatment with a single drug This was obvious from the pretreatment BP levels and from the favorable BP reduction with only small to moderate doses of the two drugs used The doses of bendroflumethiazide and propranolol were chosen to give the same BP reduction which was in fact achieved Differences between the groups treated with the two drugs are therefore not attributable to differences in BP reduction

A shortened OGTT was used with determination of blood glucose before and 60 min after the glucose load In a small subsample ($n=14$) and in a larger group of 50 year old normotensive subjects ($n=41$) blood sugar was determined after 30 60 90 and 120 min The linear correlation coefficient was calculated between these values and the sum of blood glucose values at these 4 points of time Blood glu

cose after 60 min correlated best with the sum of blood glucose $r=0.95$ (5)

The significant fall in BP between the three measurements before treatment started is consistent with previous findings (13) The two drugs were equally effective as antihypertensive agents in the doses used and their usefulness must therefore be judged from the frequency of side effects One subject on the diuretic had to be withdrawn from treatment during the study due to side-effects that were probably related to the treatment and five subjects on propranolol treatment were withdrawn on account of side effects However three of the latter withdrawals were due to excessive tiredness which might not be drug specific Tolerance of the two agents also seemed to be equally good when judged from the decrease in the frequency of reported symptoms during the course of treatment

Metabolic side effects were studied thoroughly in order to evaluate the risk of such events during bendroflumethiazide treatment Glucose tolerance improved during 12 months treatment with both agents while there were no clinically significant changes in fasting blood sugar insulin or triglyceride concentrations The improved glucose tolerance during long term diuretic therapy has to our knowledge not been described before but there are reports of facilitation of glucose uptake into muscle (24) and inhibition of insulin release (20) during short term β blockade These latter findings are consistent with our results after 2 months propranolol treatment showing an improvement of glucose tolerance and a decrease in the fasting insulin concentration However after prolonged treatment (for 12 months) plasma insulin had returned to the pretreatment level which was significantly higher than that of normotensive subjects of the same age and sex (5) It has not been possible to study the mechanisms causing the improved glucose tolerance but the parallel improvement in the two groups may indicate that the improvement is bound to the BP reduction per se rather than to other specific effects of either of the agents

The fact that there were no changes in serum potassium or total body potassium during bendroflumethiazide treatment might be attributed to the inclusion of 0 57 mg potassium in each Salures K tablet The rise in serum potassium during propranolol treatment cannot be adequately explained but a possible mechanism is an effect mediated through the previously described decrease in plasma renin activity during propranolol therapy (19) leading to decreases in aldosterone excretion and in renal potassium losses The increase in serum uric acid with both drugs is consistent with previous findings (4 12) The absolute increases were however small and the clinical importance of these findings cannot be assessed

The finding that subjects with initial high fasting blood sugar and poor glucose tolerance were those who improved most with both types of treatment is difficult to evaluate It may be caused by drug effects The relationship may also be at least partly explained by regression towards the mean i e subjects with high initial values tended to decrease in fasting blood sugar and subjects with low initial values tended to increase

The present results however do not support the previous clinical opinion that diuretic agents must be avoided in patients with impaired glucose metabolism

The follow up period was prolonged to 24 months to try to verify the unexpected findings regarding glucose metabolism The results which after 2 years treatment were the same as after 1 year strongly corroborate the findings

The decrease in the frequency of reported symptoms during the course of treatment with both drugs cannot be properly evaluated as no untreated or placebo treated group of hypertensive subjects was followed in the same way However the finding suggests that the two drugs do not induce excessive symptoms and that both are well tolerated by patients during long term treatment

Bendroflumethiazide and propranolol seemed to be equally useful as antihypertensive agents as judged from the BP reduction and the frequency of subjective and metabolic side effects It must be born in mind however that β blocking drugs might have cardio-protective effects (1 30) other than their antihypertensive effect which also may be valuable in hypertensive patients There is a risk of inducing diabetes mellitus with bendroflumethiazide as shown by the fact that one subject out of 53 developed this disease during treatment However the fear of impairment of glucose metabolism and the potassium balance during diuretic therapy seems to have been exaggerated as no disturbances in these variables were found during bendroflumethiazide treatment in this study

At present the low cost of diuretic drugs as compared with the adrenergic β blocking drugs must be

taken into account when chosing between these two agents for antihypertensive treatment However, the repeated laboratory controls necessary during treatment with diuretic drugs render an economic comparison difficult At present there seem to be no solid grounds for preferring one type of drug to the other

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Is the Use of Hypnotics, Sedatives and Minor Tranquillizers Really a Major Health Problem?

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ABSTRACT An analysis has been made of individual purchases of hypnotics, sedatives and minor tranquillizers made during 1973 by patients who had bought such drugs either only once (group S, $n=417$) or regularly (group R, $n=76$) during a 16-month period five years earlier from pharmacies in the town of Ostersund, county of Jamtland, Sweden By 1973, 17% of the patients in each group had either died or moved out of the county and were therefore excluded from the comparison In group S, 81 patients (23%) bought the above drugs once or more in 1973, while the corresponding figure for group R was 55 (87%) Compared with 1968–69, there was a decrease in the number of prescriptions and also in the number of tablets obtained per individual Furthermore, the number of tablets per prescription was lower in 1973 Among the drugs prescribed, benzodiazepines dominated during both periods, followed by barbiturates In 1973 there was a substantial increase in the use of nitrazepam, mostly at the expense of diazepam and combined products One patient in group S and one in group R showed a tendency to decrease the interval between purchases The latter was already known to be a drug abuser five years earlier Without knowing the reason why the drugs were prescribed and to what extent they were actually taken, it is impossible to say whether the other patient should be classified as drug abuser or not Although the number of patients in this study is limited, it might be concluded that the risk of an occasional user of hypnotics, sedatives and minor tranquillizers living in this area becoming an abuser of such drugs within a five-year period is less than 1/345

In March 1968 a system of continuous individual registration of drugs obtained on prescription was started in the town of Östersund county of Jamtland in western Sweden (2 3) Initially 1/15 (3 000 persons) of the population of Ostersund was monitored but in 1970 the investigation was extended to cover 2/15 (17 000 persons) of the population of the county of Jamtland (6)

An analysis of the prescriptions in the period March 1968 – June 1969 showed that 878 of the patients had obtained sedatives hypnotics and minor tranquillizers from pharmacies in Ostersund (4) Hypnotics sedatives and minor tranquillizers are available in Sweden only on prescription Four hundred and seventeen patients obtained only one prescription for such drugs during the 16-month period studied while 76 received at least one prescription every two months The two groups were similar with regard to the number of tablets of hypnotics sedatives and minor tranquillizers per prescription but the latter group obtained major tranquillizers and antidepressants to a greater extent

Since there has been much concern about the use and abuse of hypnotics sedatives and minor tranquillizers we decided to follow up these two groups of patients five years later with regard to their purchases of such drugs

MATERIAL AND METHODS

Data from prescriptions presented at the pharmacies by persons born on four chosen days each month are compiled continuously in drug lists These contain information about the patient s identity number (denoting i a age and sex) the week the drug was purchased the dispensing pharmacy the prescribing doctor the total amount dosage and price of the drug and the type of prescription (e g telephone original or repeat prescription) The method is to be presented in detail in a forthcoming publication (6)

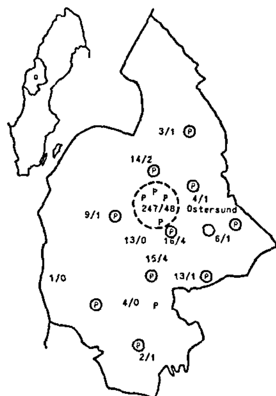


Fig 1 Map of the county of Jamtland and its location in Sweden (upper left corner) *P*=location of the pharmacies in 1968–69 Fractional numbers=place of residence and no of persons in either group (S/R)

The present investigation concerns patients born on two chosen days each month and presenting either only one (group S) or eight or more (group R) prescriptions for hypnotics sedatives or minor tranquillizers at the pharmacies in Östersund during the 16-month period March 1968 – June 1969

An analysis was made of the drug lists for 1968–69 and 1973 for some patients also the lists for 1970–73 The drug lists for 1970–73 contain information on prescription drug purchases in the whole county, and for 1968–69 in Östersund only For patients who did not obtain any drugs on prescription in 1973 a check was made in the Population Register to see whether they were still living in the county If a patient had died the cause of death was obtained from the parish authority

RESULTS

The material from 1968–69 comprised 417 patients in group S and 76 in group R (Table I) The percentage of patients no longer living in the county in 1973—the same for both groups—and the reasons for excluding them from further comparison are given in Table I Of those remaining in the county 247 (72%) in group S and 48 (76%) in group R lived in or near the town of Östersund the others outside Östersund but still within the county of Jamtland (Fig 1)

Of the patients still living in the county 23% in group S bought hypnotics sedatives and minor tranquillizers in 1973 The corresponding figure for group R was 87% (Fig 2) The number of prescriptions was 0–7 in group S and 0–80 in group R (Table II) Compared with 1968–69 there was a decrease in the number of prescriptions in 1973 The difference was highly significant ($p<0.001$) for men and women in group S and for women in group R For men in the latter group the difference was not statistically significant on account of one man s increase from 30 purchases in 1968–69 to 80 in 1973

Table I *Number of original members of groups S and R (1968–69) in drug lists and in the County Population Register in 1973 and persons no longer living in the county*

Figures within parentheses denote percentages

	Group S			Group R		
	Men	Women	Total	Men	Women	Total
Living in county						
Purchased drugs on prescription	91	162	253 (61)	24	35	59 (78)
Did not purchase drugs on prescription	42	50	92 (22)	1	3	4 (5)
No longer living in county						
Dead*	21	13	34	4	5	9
Moved out	18	20	38	3	1	4
Total	39	33	72 (17)	7	6	13 (17)
	172	245	417	32	44	76

* Cause of death neoplasm 8 blood disorder 2 circulatory disorder 26 respiratory disorder 1 gastrointestinal disorder 2 suicide 4

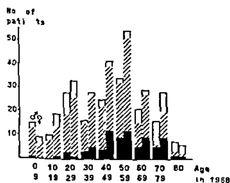
Table II *Number of prescriptions for hypnotics sedatives and minor tranquillizers per patient in groups S and R in 1973*

No of prescrip-tions	Group S (no of pats)		Group R (no of pats)	
	Men	Women	Men	Women
0	102	162	2	6
1	19	31	5	7
2	3	7	4	
3	4	4	3	5
4	4	4	2	3
5		1	2	7
6–10	1	3	6	5
11–15				4
21				1
80			1	
Mean in 1973	0 45	0 46	6 6	4 7
Mean in 1968–69*	0 75	0 75	10 5	9 2
Range in 1968–69*			6–29	6–19

Corrected for the longer observation time – 16 months

There was also a decrease in the average number of tablets obtained per individual (Table III) A sign test shows that these differences are significant at the 0 1% level for both groups Furthermore the number of tablets per prescription was lower in 1973 (Table IV) Based on the number of prescriptions benzodiazepines dominated both groups both in 1968–69 and in 1973 followed by barbiturates Percentagewise there was a substantial increase in the use of nitrazepam in 1973 mostly at the expense of diazepam and combined products (Table V) Compared with 1968–69 there was a decrease in the number of repeat prescriptions in 1973 while the number of prescriptions ordered by telephone increased

From information about the number of tablets prescribed and the dosage it was possible to estimate how long the tablets obtained on each occasion should have lasted In group S only one patient showed a tendency to shorten the intervals between refills Without knowing the patient s medical history and the reason why the drugs were prescribed it is impossible to judge whether this indicates abuse or not In group R three individuals had reduced the intervals between purchase or increased the amounts obtained in 1973 compared with 1968–69 In two patients the increase was insignificant The third patient was known already in 1968 to be a drug abuser a psychiatrist is now pre



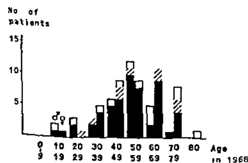


Fig 2 Age and sex distribution of patients in group S (top) and group R (bottom) in 1968–69 and 1973 ■= purchased hypnotics sedatives or minor tranquillizers in 1973 ▨=*did not* purchase hypnotics sedatives or minor tranquillizers in 1973 □=not living in the county in 1973

Table III *Average number of tablets purchased per patient per month*

Range within parentheses

Period	Group S	Group R
1968–69	5 4 (1 3–15 6)	82 9 (31 3–173 1)
1973	3 9 (0–43 8)	37 3 (0–317 5)

Table IV *Percentage distribution of the number of tablets per prescription for patients in groups S and R*

No of tablets per prescription	Group S 1968–69	Group S 1973	Group R 1968–69	Group R 1973
250–300	1	1	1	1
200	3	0	5	7
150	1	0	1	0 3
100	60	46	67	43
50–60	21	27	17	24
25–40	11	19	6	18
10–20	23	6	3	7
5		1	0	0
	100	100	100	100

scribing the drugs required for only one or two weeks at a time Five other persons in group R were registered by the county authorities as drug abusers a term not strictly defined Three of them were in the register before 1968–69 two were entered in 1973 but the evidence in one case was not very strong All five reduced their purchases of hypnotics–sedatives by 10–50% during the observation period

Four patients two in each group had committed suicide A summary of these patients medication is given in Fig 3 With the exception of case 4 there does not seem to have been any overmedication

DISCUSSION

concern has been shown about the risk of of hypnotics sedatives and minor tranquilizers (1 5 7 8 9) but there seem to be no reliable estimates of the size of the risk The reported cases probably represent only a fraction of the total and therefore, no valid conclusions can be drawn from figures showing the number of reports in relation to the amounts of drugs prescribed or sold The only way to obtain reliable estimates of the risk is to follow a defined population over a number of years as has been done in the present study

Possible sources of error in our data must be recognized The registration of drug purchases in 1968–69 covered only the four pharmacies in the Östersund area while in 1973 all pharmacies in the county of Jamtland were included in the survey Almost 30% of the patients lived outside Östersund It is likely that these patients obtained drugs also from pharmacies outside Östersund but within the county of Jamtland in 1968–69 and that these purchases were not recorded The risk of missing purchases in 1973 is less since the whole county

Table V *Percentages of hypnotics sedatives and minor tranquillizers prescribed in 1968–69 and 1973 calculated on the number of prescriptions*

	Group S 1968–69	Group S 1973	Group R 1968–69	Group R 1973
Barbiturates	14 5	10 6	14 1	12 3
Piperidinedione derivatives	1 2	0	1 0	2 9
Propanediol derivatives	3 6	0 6	4 6	4 0
Benzodiazepines	41 5	59 6	44 1	49 4
Chlordiazepoxide	9 7	5 6	9 1	7 7
Diazepam	29 4	11 8	26 8	10 7
Nitrazepam	2 4	36 6	2 9	23 0
Oxazepam	0	5 6	5 3	8 0
Alcohols aldehydes	3 6	0	0	0
Antihistamines with sedative effect	2 8	6 2	1 6	3 2
Methaqualone	0 4	0	0 1	3 4
Combined products	31 9	22 4	34 5	24 8
	100	100	100	100

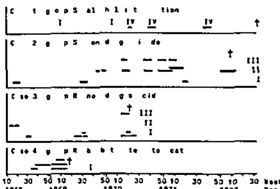


Fig 3 Drug purchase pattern of four patients who committed suicide Length of line=no of weeks the prescribed drugs should have lasted Broken line denotes that the dosage instructions were "as required" *I* hypnotics sedatives and minor tranquillizers *II*=major tranquillizers *III*=tricyclic antidepressants *IV*=analgesics combined with sedatives

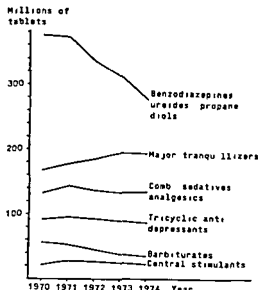


Fig 4 Sales of psychotropic drugs in Sweden in 1970–74

was included The number of prescriptions not coded in 1973 corresponds to 1 9% The number of patients residing in the area who collect their drugs from pharmacies outside the county is negligible

If some prescriptions were missed during the first registration period, this would further accentuate any increase in drug purchases during the latter period However it was found that both groups had *reduced* the amounts of hypnotics sedatives and minor tranquillizers collected at the pharmacy in 1973 compared with the period five years earlier Thus viewing the drug purchase pattern in the two groups as a whole the findings do not indicate any development of abuse

Prescription data do not tell us *why* the drugs have been prescribed or *if* and *how* they have been taken—important information in cases where abuse is suspected In the present investigation nothing is known about the extent to which the purchased drugs were actually consumed Furthermore no attempt has been made to investigate the drug pattern of the individuals who left the county between the two study periods (38 in group S 4 in group R) Bearing in mind these reservations it seems justifiable to conclude from our data that the risk of an occasional user of hypnotics sedatives and minor tranquillizers living in this area becoming an abuser of such drugs within a five year period is less than 1/345 It also seems justifiable to conclude that patients who regularly obtain hypnotics sedatives and minor tranquillizers on prescription can reduce their consumption

The decrease in the number of tablets prescribed on each occasion and in the number of repeat prescriptions might be a result of the discussion in 1971–72 in the Swedish medical and lay press on an assumed overuse of hypnotics sedatives and minor tranquillizers Sales of these drugs have decreased not only in Östersund but in the country as a whole (Fig 4) Whether or not we have now reached an optimal level of use is not known

It is important to continue the follow up of the patients in this study to see how their pattern of drug consumption develops However it will probably be necessary to study larger populations in order to obtain reliable estimates of the risk of abuse From 1970 the registration covers 1/7 of the population of the county of Jamtland i e six times the population covered in the present study A similar follow up of these patients is the next step

ACKNOWLEDGEMENTS

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The Effect of Different Oral Anticoagulants on Diphenylhydantoin (DPH) and Tolbutamide Metabolism

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ABSTRACT The effect of bishydroxycoumarin phenprocoumon warfarin and phenindione on the metabolism of diphenylhydantoin (DPH) and tolbutamide has been studied in 54 patients The half lives of DPH and tolbutamide in blood following i v injections were studied in 33 patients before and after one week of anticoagulant treatment Bishydroxycoumarin increased the mean half life values of DPH from 8 8 to 37 4 hours and of tolbutamide from 4 9 to 17 5 Phenprocoumon prolonged DPH half life from a mean value of 9 9 to 14 0 hours but did not change the tolbutamide half life Warfarin and phenindione did not affect DPH or tolbutamide half lives Steady state concentration studies in 21 patients showed a rise in serum DPH during bishydroxycoumarin and phenprocoumon treatment but not during treatment with warfarin and phenindione A rise in serum tolbutamide was noted during treatment with bishydroxycoumarin These findings suggest that bishydroxycoumarin inhibits the metabolism of DPH and tolbutamide and that phenprocoumon inhibits DPH metabolism No effect on DPH and tolbutamide metabolism could be demonstrated following administration of warfarin and phenindione

Many drugs have been shown to interact with oral anticoagulants and several of these drug interactions are clinically important (9 10 13) We have previously demonstrated that bishydroxycoumarin inhibits the metabolism of diphenylhydantoin (DPH) and tolbutamide (8 11) in contradiction to phenindione Whether other commonly used oral anticoagulants such as warfarin and phenprocoumon influence drug metabolism has not yet been studied

MATERIAL AND METHODS

The material comprised a total of 54 volunteers consisting of patients admitted to hospital for neurological functional and arteriosclerotic diseases and 6 patients with maturity onset diabetes None did receive other medicaments than the drugs tested during the study

Sixteen patients were given 1 g tolbutamide i v before and after one week of anticoagulant treatment with bishydroxycoumarin (8 pats) phenindione (3 pats) warfarin (2 pats) or phenprocoumon (3 pats) The tolbutamide concentration was determined at intervals during the 24 hours following the injections the first sample being taken two hours after the injection and another four samples at equidistant intervals The half life of tolbutamide in blood was determined from these values

Seventeen patients were given 100 mg DPH to which 20 μCi 4-^{14}C labelled DPH had been added before and after 1 week of anticoagulant treatment with bishydroxycoumarin (3 pats) phenindione (5 pats) warfarin (4 pats) or phenprocoumon (5 pats) The half life of DPH in blood was determined by measuring the radioactivity of extracts of serum from blood samples taken approximately 3 6 9 and 12–27 hours after injection The extraction procedure has been described in detail previously (7) On thin layer chromatography serum radioactivity was found only corresponding to the position of DPH

The error of DPH and tolbutamide half life determinations has been estimated by two half life determinations at a 10 days interval in 10 patients and the coefficient of variation was 9% and 10% respectively

Four diabetic patients on a constant tolbutamide peroral dose were also given bishydroxycoumarin perorally and blood samples for tolbutamide determination were taken before and three hours after tolbutamide administration Two diabetics were studied in a similar way after warfarin medication

In a total of 15 patients on a constant dose of 300 mg DPH perorally serum DPH was estimated every third day before and during a period of 1 week on anticoagulant treatment perorally with bishydroxycoumarin (5 pat)

Table I *Mean values for half lives of DPH and tolbutamide before and during treatment with anticoagulants (range given within parentheses)*

	No of pats	DPH half life (h)		No of pats	Tolbutamide half life (h)	
		Before	During		Before	During
Bishydroxycoumarin	3	8 8 (7 7–9 8)	37 4 (33 8–44 0)	8	4 9 (2 8–6 5)	17 5 (10 0–25 0)
Phenprocoumon	5	9 9 (5 9–18 0)	14 0 (9 7–29 5)	3	5 0 (4 5–5 5)	5 3 (4 5–6 0)
Warfarin	4	11 6 (8 7–15 3)	11 1 (9 3–12 3)	2	4 5 (4 5–4 5)	5 0 (5 0–5 0)
Phenindione	5	13 0 (9 0–22 5)	13 6 (10 0–19 8)	3	5 5 (3 8–6 8)	6 0 (5 3–6 8)

phenindione (4 pats) warfarin (2 pats) and phenprocoumon (4 pats)

All the patients had anticoagulant medication with conventional doses adjusted to give prothrombin proconvertin values within the therapeutic range The oral anticoagulants and the long term DPH treatments were given on therapeutic indications and the single i v doses of tolbutamide and DPH were given experimentally with the patients consent

The tolbutamide concentration was determined by the method of Spingler (14) and serum DPH by the method described by Dill et al (6) None of the anticoagulant drugs studied did interfere with the tolbutamide or DPH analyses

RESULTS

highly significant increase in the half lives of tol ide and DPH occurred during bishydroxy marin treatment ($p<0\ 001$) and the mean values both drugs were prolonged about four times (Table I) No changes in the half lives of tolbutamide could be demonstrated during treatment with

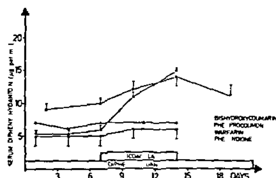


Fig 1 Serum DPH before and during anticoagulant treatment with bishydroxycoumarin (5 pats) phenindione (4 pats) warfarin (2 pats) and phenprocoumon (4 pats) (mean ±S E M)

phenprocoumon but the half life of DPH increased about 40 % which was significant with a paired *t* test ($p<0\ 05$) The half lives of tolbutamide and DPH were unaffected by treatment with warfarin and phenindione

Serum concentrations of DPH before and during treatment with the four anticoagulants tested are shown in Fig 1 An increase in serum DPH was noted after a few days treatment with bishydroxy coumarin and phenprocoumon No changes in serum DPH occurred during treatment with warfarin and phenindione

Serum tolbutamide was also determined before and during bishydroxycoumarin treatment In four patients the fasting serum tolbutamide increased from an average of 0 4 to an average of 7 0 mg/100 ml following one week s treatment with bishydroxycoumarin A simultaneous decrease in fasting blood sugar was noted Serum tolbutamide was determined in two patients before and after treatment with warfarin for one week and no change in the low fasting serum tolbutamide concentrations was observed

DISCUSSION

As shown previously, bishydroxycoumarin acts as an inhibitor of tolbutamide and DPH metabolism (8 11) These interactions have since been proven to be of clinical importance The authors are aware of four cases of severe hypoglycemia and DPH intoxication provoked by these drug combinations

In the present study the effect of other anticoagulants (phenprocoumon warfarin and phenindione) on the metabolism of tolbutamide and DPH has been evaluated Phenprocoumon seems to inhibit the metabolism of DPH but to a much smaller

degree than bishydroxycoumarin However the possibility of DPH intoxication in patients receiving both drugs should be considered The authors are not aware of clinical reports on this drug interaction The fact that phenprocoumon affects DPH half life but does not inhibit the metabolism of *tolbutamide is not readily explained* since bis hydroxycoumarin increases the half life of both drugs to the same degree

Furthermore it has been shown in previous studies that other drugs such as phenylbutazone oxyphenbutazone sulphaphenazole (1 4 8) and chloramphenicol (5) are able to inhibit as well tol butamide as DPH metabolism It is generally as sumed that both DPH and tolbutamide are metabolized in the microsomal drug metabolizing en *zyme system of the liver (2 15) We have previ* ously suggested that bishydroxycoumarin acts as an inhibitor of this system and later studies using rat liver microsomal enzymes (3) have shown that dicoumarol and related compounds have an inhibitory effect on the activity of some oxidases of rat liver The effect of bishydroxycoumarin warfarin and phenprocoumon on anilin hydroxylase was almost identical using the same molar concentration

Our results suggest that coumarins though chemically related might have a different action on the microsomal enzyme systems However the commonly used doses of phenprocoumon and warfarin are much smaller than those of bishydroxy coumarin giving a smaller molar concentration in the body tissues Furthermore bishydroxycoumarin is known to have dose dependent half life in con trast to warfarin (12) and this might also add to the difference in inhibition of DPH metabolism These factors might partly explain the different action of the coumarins on DPH and tolbutamide metabolism The chemical configuration of phenindione differs so much from the coumarins that this could explain the difference The drug interactions described in this paper must be considered when patients receiving DPH and tolbutamide are given anticoagulants

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Attempted Suicide with 5 1 g of Propranolol

A Case Report

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Only a few attempted suicides with β receptor blocking agents (BBA) have been reported and in only one case have the symptoms described been life threatening (5 6 8) This has led some ob servers to suggest that the effects of propranolol on the healthy heart need to be reconsidered (8) However this case report of a man who attempted suicide by taking 5 120 mg propranolol reveals symptoms serious enough to be fatal Rare as their occurrence may be, we feel that they deserve care ful consideration by all physicians prescribing BBA

CASE REPORT

A 41 year old former personnel manager with alcohol problems was admitted to hospital after ingesting 32 tablets containing 160 mg propranolol each He arrived at the emergency room approximately 100 min after the act On arrival he was cyanotic had a weak pulse with a rate of 50 beats/min his BP was unobtainable and he ex hibited generalized intermittent convulsions Spontaneous respiration had not ceased and upon being given oxygen by mask his colour improved markedly He was im mediately transferred to the Medical Intensive Care Unit (ICU) Upon arrival at the ICU he was comatose and the convulsions continued to occur at 1 5 minute intervals lasting for 15-30 sec each The radial pulse was barely noticeable and the ECG showed a supraventricular bradycardia without identifiable P waves

Atropine 0 5 mg and epinephrine 1 mg were injected without noticeable effect on the heart rate and 5 mg iso-proterenol in 500 ml 5 5% glucose was administered by i v drip at maximum speed

Shortly thereafter the pulse rate dropped further to asystole External cardiac massage was immediately started an orotracheal tube was inserted and connected to an Engstrom respirator and alcuronium was injected to stop the convulsions Further injections of 0 5 mg epinephrine were given at 5 min intervals resulting after approximately 20 min in regular cardiac activity as seen on the ECG monitor The peripheral pulse at this time was however still barely perceptible with a rate of 50-60 beats/min and external cardiac massage was therefore continued

A transvenous pacemaker was then inserted via the left subclavian vein Technical difficulties were encountered and the electrode was caught up in the right atrium From there it was however possible to initiate regular ventric ular rhythm thereby demonstrating patency of atrio-ventricular conduction Repeated attempts to enter the ventricle were finally successful and after 37 min it was possible to discontinue external cardiac massage

The peripheral pulse was however still unsatisfactory and not until an i v drip containing 20 mg isoproterenol in 500 ml 5 5% glucose was given at a rate of 0 6 ml/min corresponding to 25 μg/min and further injections of epinephrine were administered was a BP reading of 130/90 mmHg obtained At this time a total of 6 mg epinephrine had been given over a period of exactly 60 min

Arterial blood gases showed a combined metabolic and respiratory acidosis with a base deficit 15 mEq/l blood glucose was 264 mg/100 ml SGOT 86 and SGPT 57 U and ethanol concentration was 1 5‰ Otherwise labora tory data were normal

He remained in a deep coma with dilated pupils not responding to light for several hours Respirator treat ment was discontinued after 18 hours and two hours later the orotracheal tube was removed Arterial blood gases at this time were within normal limits as were other labora tory data

During the next two days the pacemaker was required to maintain cardiac frequency Satisfactory circulation was achieved only when combined with a total of 40 mg isoproterenol in 5 5% glucose/24 hours The pacemaker was removed after 62 hours and the isoproterenol drip was discontinued after 65 hours during which period a total of 115 mg as a continuous infusion had been ad ministered His physical condition continued to improve and after one week he was transferred to the Department of Psychiatry for further treatment At this time he was fully mobilized and had no apparent sequelae after the protracted circulatory arrest He did however suffer from amnesia for the hours immediately preceding and in cluding the attempted suicide

DISCUSSION

Of the three attempted suicides with BBA found in the literature (5 6 8) two exhibited only very mild symptoms requiring nothing but careful super vision and in one case gastric lavage The third case recovered after one dose of i v glucagon (6) Our patient exhibited severe bradycardia which eventually progressed to asystole severe hypotension and generalized intermittent convulsions This is then by far the most serious case of self poisoning with BBA reported to date

Bradycardia and hypotension are manifestations of the known pharmacologic actions of BBA That these manifestations can be life threatening as in our patient and in rare cases even fatal is well known (4 7)

Isoproterenol has a positive inotropic and chronotropic effect on the myocardium It has been demonstrated that this effect can be blocked by varying doses of BBA (2 6) though perhaps this block is only relative since only medium doses of isoproterenol were used in these studies Our patient exhibited an extraordinary resistance to isoproterenol Satisfactory cardiac contractility was achieved and maintained only with the aid of massive doses of isoproterenol and epinephrine Even so the chronotropic action was not satisfactory necessitating a transvenous pacemaker

The same studies (2 6) have however presented suggestive evidence that this block can be by ...sed by the administration of glucagon It has ... postulated that this is due to the presence of ...ifferent receptor types in the adenyl cyclase system one that is activated by catecholamines and one by glucagon Greenblatt and Koch Weser (3) studied 268 patients who received propranolol during one or more hospital admissions Of the 25 reported adverse reactions 4 were neurological disturbances These consisted of drowsiness light headedness dizziness blurring of vision and diaphoresis in various combinations No cases of convulsions were reported

Barar and Madan (1) studied the effects of BBA on spontaneous motor activity in mice They found that propranolol had a significant CNS depressant action When given in lethal doses death was preceded by convulsions marked increase in respiratory rate and exhaustion The convulsions thus appear to be a consequence of the CNS depression To our knowledge this is the first time that generalized convulsions due to overdosage with BBA have been reported in humans Whether such convulsions should be treated with the usual anticonvulsants or with muscle relaxants has yet to be determined but since they appear to be the consequence of CNS depression we feel that muscle relaxants are to be preferred

Our experience from this case and the literature survey suggest the following treatment principles for propranolol overdosage 1) Gastric lavage charcoal instillation continuous ECG monitoring 2) Glucagon 1–5 mg i v 3) Isoproterenol in doses high enough to maintain cardiac contractility 4) Transvenous pacemaker 5) Convulsions should be treated with muscle relaxants orotracheal intubation and artificial respiration

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Pericardial Angiomatosis

A Case Report

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ABSTRACT A case of cardiac tamponade following bleeding from an angiomatous plexus on the surface of the pericardium is described

Diseases of the pericardium are rare and usually accompanied in the acute stages by pericardial effusion Such an effusion may be blood stained if the acute inflammatory changes are severe However persistent blood staining is commonly regarded as an indication that the effusion may be due to the presence of malignant tumour cells In the vast majority of cases this tumour growth is metastatic Primary malignant cardiac tumours are very rare but when present often accompanied by haemopericardium (1)

The present case had an unusual clinical history with a persistent blood stained pericardial effusion At necropsy the bleeding was found to arise from a diffuse capillary plexus on the surface of the pericardium for which the descriptive term pericardial angiomatosis has been used The term has been used previously to denote multiple discrete haemangiomata of the pericardium (2) The aetiology is discussed

CASE REPORT

The patient a man of 47 years had an attack of poliomyelitis when 19 years old with minimal transient paralysis in both legs Six years later he developed acute nephritis with moderately raised blood pressure He was followed up as an out patient for the next 5 years From then until his final illness he was well and led an active life On the day of admission to hospital he developed sudden crushing pain in the epigastrium radiating into the neck and chest He complained of nausea dizziness headache and later dyspnoea The latter complaints cleared up within a few hours but the chest pain continued He contacted the local emergency service and an ECG showed changes suggestive of an acute anterior wall infarct

On admission he complained of chest pain but was in relatively good physical condition His BP was 135/100 mmHg pulse 112/min regular with no pulse deficit temperature 37 9°C ESR 15 mm The ECG on admission was *indicative of pericarditis but infarction could not be excluded* There was congestion of the neck veins at 45 and the liver was just palpable An aortic systolic murmur was present but no pericardial friction rub

A tentative diagnosis of viral myocarditis or pericarditis was made However in view of the ECG findings he was treated with anticoagulants His progress was uneventful until 5 days later when the BP suddenly fell and he became shocked Supportive treatment was instituted The absolute heart volume on X ray (700 ml relative 980 ml/m²) indicated a developing cardiac tamponade Anti coagulant treatment was stopped Vitamin K was given parenterally and the thrombotest became normal within a few days On the seventh day 345 ml of grossly blood stained fluid were tapped from the pericardium His condition subsequently improved and a systolic and diastolic pericardial friction rub appeared Eight days later a further 600 ml of fluid were tapped with good clinical effect This fluid was less blood stained than previously It was examined bacteriologically virologically and cytologically but no positive results were obtained During the next weeks the patient gradually recovered the ECG changes almost disappeared the heart volume returned to the upper limits of normal (absolute volume 980 relative 540 ml/m²)

After 17 days of uneventful convalescence he suddenly collapsed while standing washing External cardiac massage was without effect and he died approximately 4 weeks after the start of his illness

Necropsy (O 113/75–13 hours post mortem)

The body was that of a man weighing 64 kg The major findings were confined to the heart and the pericardium No evidence of a primary malignant tumour was found

The heart weighed 530 g The pericardial sac contained 400 ml of freshly clotted blood This was considered the

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Fig 1 Surface of pericardium Note Irregular folding of the surface forming villous like projections covered with pericardial cells and consisting of a well vascularized loose connective tissue matrix continuous with the subpericardial alveolar tissue at bottom of the picture H+E ×21

Fig 2 Surface of pericardium Note Haemorrhage from the vascular plexus in a villous like projection from the pericardial surface H+E ×21

Fig 3 Surface of pericardium Note Alveolar connective tissue (bottom) with vascular connections (bottom right) to the overlying fold of highly vascular alveolar tissue H+E ×54

Fig 4 Epicardial fat with vascular plexus on surface Note Myocardium (bottom left) fatty tissue with minimal reactive changes over this pericardial surface (top right) Plexus of well developed capillaries and arterioles running parallel and perpendicular to the surface in a layer of condensed alveolar tissue continuing beneath the pericardial surface H+E ×54

immediate cause of death There was no perforation of the myocardium The bleeding appeared to have come from multiple bleeding points on the pericardial surface (Fig 2) The whole surface over the heart and fibrous pericardium was dark red with a wet velvety appearance This was interpreted macroscopically as a diffuse pericarditis There were loose adhesions between the layers towards the base of the heart

A calcified aortic stenosis of mild degree was present and the left ventricle showed slight hypertrophy Apart from this the myocardium showed no abnormality macroscopically or microscopically The mitral valve had slightly thickened cusps but the chordae were normal The endocardium over MacCallum s patch was microscopically thickened with signs of previous rheumatic disease The aortic stenosis may thus have been of rheumatic origin The coronary arteries showed mild atherosclerosis but were not markedly narrowed Bacteriological and virological investigations were negative

Interpretation of the microscopical findings in the pericardium proved difficult Formalin fixed paraffin embedded blocks were stained with a variety of stains including haematoxylin and eosin Mallory s PTAH AB PAS Elastin van Gieson and Toluidine blue and Berliner blue

Microscopically the band of loose areolar connective tissue covered by a single layer of flat cells as on the surface of the normal pericardium could be identified in all sections lying in places directly on the myocardial cells or separated from them by a layer of epicardial fatty tissue While the normal level of the pericardial surface could thus be identified in places the endocardial cells and areolar connective tissue over the major part of the surface were thrown up into irregular folds or villous like projections (Fig 1) The base of these folds contained well developed blood vessels surrounded by a thin layer of areolar tissue (Fig 3)

The epicardial tissues contained a well developed plexus of capillaries and arterioles (Fig 4) with plump endothelial cells In places the vessels ran parallel to the surface of the heart in others they passed directly into the villous like projections

The pericardial surface was thus shaggy and covered by a layer of pericardial cells except where bleeding had occurred and the surface was eroded (Fig 2)

Apart from the acute haemorrhage in these areas reactive changes were minimal Iron-containing macrophages and scattered lymphocytes were present in some areas mainly in the villous folds The deeper layers under the normal pericardial level showed little evidence of inflammatory change either old or new There was no fibrosis or scarring and stains for fibrin were negative Granular material that stained with PAS and was metachromatic with Toluidine blue was however found in the pericardial alveolar connective tissue both in the folds and deeper layer Closer inspection showed that this was derived from partly degranulated mast cells related to the vascular plexus

The cause of death was thus considered to be bleeding from the vascular plexus in the pericardium with resultant acute cardiac tamponade On cutting down blocks from the surface of the pericardium it appeared that the larger vessels of the plexus were probably derived from branches of the coronary arteries but a direct connection was not demonstrated

DISCUSSION

The pericardial effusion and subsequent fatal haemorrhage in the present case arose from an angiomatous plexus on the surface of the pericardium

The histological findings are in keeping with the clinical history if one interprets the first acute episode as a very minor bleeding from the plexus and the second as a larger one The presence of blood in the pericardial sac could under normal circumstances be expected to lead to the formation of an inflammatory exudate The exaggerated response in the present case would be in keeping with the excessive number of vessels present on the reacting surface The lymphocytes and iron-containing macrophages found in the surface layer of the pericardium at death are evidence of these previous bleedings The patient died within minutes of his final haemorrhage Mast cell degranulation and dilatation of the smaller vessels in keeping with an immediate response to injury were the only signs of an acute inflammatory response in the pericardium

The origin of this vascular plexus is obscure Its diffuse character suggests that it could be reactive If so the manner in which it was built up with well developed blood vessels and loose connective tissue and the minimal reactive changes and complete pericardial covering indicate that it was not of recent origin The above changes are not consistent with its formation in relation to the first clinical symptoms It is also unlikely that the histological features of the present case could be the result of rheumatic inflammation of the pericardium which usually results in scarring or of a previous viral infection

If the plexus is not reactive it may be neoplastic Angiomata though very rare have been described in the pericardium The majority are of cavernous type (4) They are usually single and discrete and are not reported to have caused haemopericardium However capillary haemangioma of the pericardium have also been reported (2) All caused death from haemopericardium Those previously reported have been discrete although one case of multiple cavernous and capillary haemangioma in a patient with a history similar to that in the present









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Postvaccinial Lymphadenitis Developing into Hodgkin's Disease

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ABSTRACT In four cases, Hodgkin's disease developed after vaccination against smallpox (three cases) and diphtheria (one case) The cases are reported and may contribute to the discussion on the aetiology and nature of Hodgkin s disease

The aetiology and nature of Hodgkin s disease are still unknown Hypotheses are many and different (infectious granulomatous disorders infections developing into malignancies true malignant tumours immunological or autoimmunological aetiology viruses acting in different ways and furthermore the theory that Hodgkin s disease may comprise more than one pathological entity) It is not my intention to discuss the possible aetiology only to add a few observations which may contribute to the postulations put forward by other investigators

In a recent review by Begemann and Kaboth (1) it is mentioned that Hodgkin s disease developed in two patients after vaccination In their chapter on aetiology it is stated Wir haben aus der Verschiedenheit der auslosenden Faktoren geschlossen dass offenbar jede Stimulierung des lymphatischen Systems durch Reizungen mit exogenen oder endogenen Substanzen meist von Antigencharakter zur Manifestierung der Lgr führen kann Liegen zwischen traumatischer Alteration und Erstmanifestation der Lgr grossere Zeitabschnitte so wird man zur Anerkennung eines Kausalnexus Bruckensymptome in Form von starkerem Hautjucken unerklärbaren oft wellenförmigen Fieberschuben oder persistierenden oder wechselnden Lymphknotenschwellungen fordern mussen In zwei Fallen mussten auch Impfungen als Realisierungsfaktor anerkannt werden

Biopsies of enlarged lymph nodes after smallpox vaccination are performed very rarely but there is an excellent review of 20 cases by Hartsock (2) who reported that 9 of 20 cases of postvaccinial lymphadenitis were submitted to the Armed Forces Institute in the United States suspected of a malignant lymphoma None of the patients died from Hodgkin s disease and Hartsock described the histological picture of postvaccinial lymphadenitis as follows (*1*) an increased number of reticular lymphoblasts imparting a mottled appearance to the lymphoid tissue (2) a diffuse folicular or combined diffuse and follicular hyperplasia, (*3*) vascular and sinusoidal changes and (*4*) a mixed cellular response The reticular lymphoblasts can be misconstrued as Reed Sternberg cells These cells have scant cytoplasm a large nucleus and one or more acidophilic nucleoli The histologic changes of these lymph nodes are not pathognomonic because similar changes occur in infectious mononucleosis herpes zoster and dermatopathic lymphadenitis

In the years 1936–39 I was in charge of the Department of Haematology at the Cancer Clinic in Århus I made some notes on my patients suffering from Hodgkin s disease (179 cases) and recently reviewed the records I have later again been involved in the diagnosis and treatment of patients with disorders of the blood and made an observation which may be relevant to the present communication

CASE REPORTS

Case 1

An 8-year old boy was vaccinated against smallpox on the left upper arm in 1937 Soon afterwards enlarged lymph

nodes appeared on the left side of the neck The swelling remained unchanged for 2½ years At that time the patient became febrile and the lymph nodes on the neck rapidly increased in size and now lymph node swelling also appeared in the left axilla and on the right side of the neck The patient was admitted to another hospital where a biopsy specimen of the now enormously increased nodes on the neck showed Hodgkin s disease

Consequently the boy at that time 11 years old was transferred to the Cancer Clinic in Århus in July 1940 The patient was emaciated febrile and very tired X ray examination of the chest disclosed enlarged hilar nodes and there was a moderate spleno- and hepatomegaly He was treated with X rays to the tumour on the left side of the neck The tumour decreased in size and the boy felt better He was discharged home in Aug 1940 and was lost sight of He died at home in Nov 1940 It has not been possible to obtain the original biopsy specimen but the description by an experienced pathologist leaves no doubt that the case was one of typical Hodgkin s disease Had it been possible to place the histological picture according to the Rye classification the diagnosis would probably have been nodular sclerosis

Case 2

A 14-year old girl was admitted to the Cancer Clinic on Feb 14 1938 Six months before admission she had been vaccinated against smallpox on the left upper arm After the vaccination she had to go to bed and enlarged lymph nodes appeared on the left side of the neck A few months later the lymph nodes of the neck increased in size and now there was also swelling of a lymph node in the left axilla She was admitted to another hospital in April 1938 and a biopsy specimen from a lymph node of the left axilla was consistent with the diagnosis of Hodgkin s disease A recent revision of the biopsy specimen confirmed that the agnosis was Hodgkin s disease (nodular sclerosis)

Shortly after the admission to the Cancer Clinic the disease became generalized and in spite of X ray treatment the patient died from her disease on April 8 1940 Autopsy revealed generalized Hodgkin s disease involving the lymph nodes of the neck mediastinum porta hepatis pancreas stomach and in the lumbar region with infiltrations in both lungs and the spleen

Case 3

A 76-year-old widow was admitted to the Cancer Clinic in Århus in Dec 1973 She had suffered from chronic polyarthritis for several years and had been treated with Sanocrysin ® in another hospital Otherwise the clinical history was irrelevant In the spring of 1972 before going to Italy she was vaccinated against smallpox in the left upper arm Immediately after the vaccination swelling of the left upper arm occurred When the swelling decreased the patient observed a small nodule in the left axilla It persisted for about a year but in June–July 1973 it increased and swelling of the lymph nodes of the left side of the neck also occurred She was admitted to another hospital and here a tumour mass was observed in the left axilla extending through the clavicular region to the left side of the neck A biopsy specimen showed sequelae after lymphadenitis with fibrosis The patient was in good health but in the beginning of Oct 1973 the tumour increased in size and a new biopsy aroused suspicion of a malignant disorder probably Hodgkin s disease

She was admitted to the Cancer Clinic in Dec 1973 and a new biopsy left no doubt that the diagnosis was Hodgkin s disease classified as mixed cellularity Lymphography was performed and several suspicious nodes were found in the lumbar and the left iliac regions The patient was classified as in stage II A and treated with combined chemotherapy When last seen in Sept 1975 she was in complete remission and there were no palpable lymph nodes

Case 4

An 18 year old woman was vaccinated against diphtheria in the (left or right?) suprascapular region in Jan 1948 The vaccination was followed by fatigue severe headache localized in the back of the head and fever In Feb the same year enlarged lymph nodes appeared on the right side of the neck The nodes increased in size and a few months later lymph node swelling also developed in the left inguinal region In June 1943 the patient was admitted to another hospital A biopsy specimen of the nodes on the right side of the neck was strongly indicative of Hodgkin s disease

The patient was transferred to the Cancer Clinic on July 2 1943 At that time she was emaciated and febrile There were enlarged lymph nodes on both sides of the neck in the right axilla and in the left inguinal region She was treated with X rays to the nodes on the right side of the neck the right axilla and the left inguinal region However the patient deteriorated rapidly and died on Sept 5 1943 Autopsy showed lymphogranulomatosis in various superficial lymph nodes the superior mediastinum and a tumour on the right iliac bone It has been impossible to find the specimens for the histological diagnosis However as already mentioned the description of the earlier lymph node biopsy indicated that the case was one of early Hodgkin s disease Furthermore it has been possible to find a needle biopsy from the left inguinal lymph node secured during the patient s stay at the Cancer Clinic The specimen is well preserved and shows typical Hodgkin s disease with numerous Hodgkin cells with large nucleoli many histiocytic reticulum cells of a malignant appearance lymphocytes eosinophils plasma cells and a few multinucleated Reed Sternberg cells It is however difficult to place the picture according to the Rye classification

DISCUSSION

All people in Denmark are vaccinated against smallpox often more than once and many against diphtheria It is then of course accidental that some vaccinated people develop Hodgkin s disease However in the cases presented here the development of lymphadenitis immediately after the vaccination and the fact that the lymphadenitis persisted

and terminated in Hodgkin s disease are rather suspicious features I have felt it of interest to report our observations as a contribution to the hypothesis that infections of lymph nodes may sometimes be a precursor of true lymphogranulomatosis and refer again to the conclusions drawn by Begemann and Kaboth which are cited in the introduction

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Interferon Therapy in Hodgkin's Disease

A Case Report

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ABSTRACT The treatment of a case of Hodgkin s disease (lymphocyte predominance, stage IV B) with exogenous i m interferon therapy is described B symptoms disappeared, diseased nodes and pulmonary infiltrations decreased in size, and laboratory values normalized Clinical improvement was associated with increased mitogenic responsiveness of the patient's lymphocytes towards various stimuli in vitro After almost half a year's treatment tumour progression and a decreased mitogenic response were again observed Interferon treatment was then abandoned and combined cytostatic courses were instituted Partial remission was achieved after 6 months of cytostatic therapy, i e 1 year after the start of treatment

Exogenous interferon administration has proved effective in the treatment of lymphomas and leukemias in mice (6 10 11) We have shown that long term high dose interferon therapy is possible in human subjects without undue side effects (15 17 18) In addition the growth of some human lymphoma lines can be inhibited in tissue cultures by adding small amounts of interferon to the medium (1) We then used exogenous interferon to treat a 24 year old man with Hodgkin s disease—stage IV B lymphocyte predominance (LP)—our aim being to establish whether such therapy would affect the clinical picture and alter the course of the disease The observations made are the subject of the present report

MATERIAL AND METHODS

The interferon was prepared from human leukocytes as described previously (4) Partial purification was achieved by the selective precipitation of contaminating proteins from a 94% ethanolic solution (4) The preparations employed contained about 10 mill reference units ml (1) and about 30 mg protein/ml

Interferon treatment

Interferon was administered i m as described previously (16 17) The doses employed were as stated in Results The patient was instructed in how to give himself the injections A few minutes after one such injection he developed chills A similar reaction was noticed previously in a patient receiving less purified interferon by the i v route (16) The reaction which subsided after about 1 hour was thought to have resulted from an accidental i v injection The patient continued to use the same preparation of interferon without disturbance Laboratory tests and examinations routinely employed during interferon therapy have been described previously (16)

Cytostatic regimen

Combined cytostatic courses (CVPP) were given with i v cyclophosphamide infusion 1000 mg for 3 hours on days 1 and 10 i v vinblastine injection 10 mg on days 4 and 7 and procarbazine 150 mg and prednisolone 30 mg daily per os during 10 days The courses were separated by intervals of 4 weeks Because of discomfort following the vinblastine injections the doses were reduced to 7 mg after 2 courses

Preparation of lymphocytes

Venous blood was drawn in heparinized syringes Lymphoid cells were separated by centrifugation of the blood on a Ficoll Isopaque gradient as described by others (13) The nucleated cells were washed by centrifugation in balanced salt solution and suspended in Eagle s minimal essential medium (MEM) After crystal violet staining about 90–95% of the cells were classified as lymphocytes

Mitogens

The contents of vials containing phytohaemagglutinin (PHA Bacto-phytohaemagglutinin M Difco Lab Detroit Mich) and poke weed mitogen (PWM Grand Island Biological Comp N Y) were dissolved in 5 0 ml of

Table I *Laboratory examinations before and during treatment with interferon and CVPP*

	ESR (mm/h)	Hb (g/100 ml)	Leucocytes/ mm³	Lymphocytes/ mm	Thrombocytes ×1000/ mm³	Albumin (g/100 ml)	Haptoglobin (mg/100 ml)	Alkaline phosphatase (μmol/l)ᵃ
Jan 1974 (before treatment)	25	13 7	11 300	1 600	265	4 6	263	5 10
March 1974 (on interferon treatment)	11	13 9	4 400	1 500	180	4 6	173	5 18
Aug 1974 (end of interferon treatment)	51	12 2	11 600	NT[b]	250	3 8	231	5 09
Dec 1974 (CVPP treatment)	15	12 5	3 100	NT	195	4 2	206	4 81

Normal values <4
[b] Not tested

MEM These solutions will be referred to as 100% of PHA or PWM Concanavalin A (Con A Sigma Chemical Comp St Louis Mo) was dissolved in MEM Purified protein derivative of tuberculin (PPD tuberculin RT 22 State Serum Institute Copenhagen Denmark) was dissolved according to the instructions of the State Serum Institute Copenhagen

Cell culture conditions

Details of culture conditions and measurements of incorporated radioactivity were published previously (2) Briefly 0 25×10⁶ lymphocytes were cultured in tubes containing 1 0 ml MEM supplemented with glutamine 100 U penicillin 150 μg streptomycin and 10% human serum (HS) from AB positive blood donors The HS had previously been decomplemented by heating at 56°C for 0 min The cells were cultured either with or without ous concentrations of mitogen After 4 days at 37°C humidified 5% CO_2 air atmosphere each culture ived 0 4 μCi of ¹⁴C thymidine (Radiochemical Centre mersham England Specific activity 54 mCi/mM) The cultures were terminated 24 hours later The radioactivity of trichloroacetic acid precipitable material was measured with a Packard scintillation counter

Cultures were set up in duplicate with or without a stimulatory agent Incorporated radioactivity was expressed as counts per minute (cpm) Values obtained in unstimulated cultures were subtracted from those obtained in corresponding stimulated cultures Mean values were calculated on an arithmetic basis

Design of lymphocyte stimulation tests

In our experience the extent of in vitro stimulation of human lymphocytes by polyclonal mitogens varies considerably from time to time Wide variations are observed even when lymphocytes from the same healthy donor are tested under identical conditions This variation in mitogen response probably does not reflect changes in the true mitogen responsiveness of the donor lymphocyte population but rather changes in culture conditions which cannot be controlled For this reason we tested the reactivity of lymphocytes from a healthy 30-year old woman each time the patient s lymphocytes were tested The mitogen reactivity of the patient s lymphocytes was expressed as a percentage of the control value The lymphocytes of the control were thus assumed to have a constant responsiveness to the mitogen

CASE REPORT

The patient a man of 23 was admitted to Karolinska Hospital in Nov 1973 During the preceding 6 years he had suffered from vasomotor rhinitis In Feb 1973 he contracted lingular pneumonia Otherwise he had always been healthy In Sept 1973 he developed a respiratory infection with progressing cough At the time of admission in Nov he complained of weakness chest pain night sweats pruritus of the lower limbs and weight loss (6 kg in 2 months)

Clinical examination revealed enlarged lymph nodes in both supraclavian fossae and axillae the largest node having a diameter of 2 cm X ray examination of the lungs showed enlarged bilateral hilar lymph nodes and infiltrations in the middle lobe on the right side X ray examination of abdomen and skeleton liver scintigraphy and lymphangiography did not reveal any pathological changes Bone marrow specimens were considered normal Biopsy specimens from the supraclavian fossae and from the hilar region showed Hodgkin s disease of histological type LP with few Reed Sternberg cells ESR was 25 mm Blood tests showed no signs of anaemia but slightly elevated WBC The serum alkaline phosphatase level was raised (5 10 μl mol/l) liver tests were normal and serum haptoglobin was elevated (263 mg/100 ml) (Table I) Laparotomy was not performed According to the Ann Arbor classification the patient was at stage IVB

These investigations took 1 month At the end of this time a new pulmonary X ray showed an increase in the infiltrations of the middle lobe and increasing infiltrations into the lower lobe on the left side and in the lingular re

Table II *X ray examination of a representative hilar node and pulmonary parenchyma infiltrations before and during treatment with interferon and CVPP*

	Hilar node (mm)	Parenchyma infiltrations (mm)	
Jan 1974 (before treatment)	31	26	19
March 1974 (on interferon treatment)	22	18	17
Aug 1974 (end of interferon treatment)	26	15	18
Dec 1974 (CVPP treatment)	0	0	0

gion of the left lung During the same period there was intensification of the patient s B symptoms

Treatment with interferon (5×10^6 U i m daily) was started on Jan 21 1974 with the patient s fully informed consent Clinical examination after 2 weeks of treatment revealed a decrease in the size of the peripheral glands the largest one now measuring 1 cm in diameter A pulmonary X ray showed a minor decrease in the pulmonary infiltrations and a small decrease in the enlarged hilar nodes After 3 weeks of treatment the patient s cough became less severe his general physical condition improved and he started to gain weight The pruritus of the lower limbs disappeared After 1½ months of interferon treatment the B symptoms has disappeared completely At the same time ESR WBC and haptoglobin values were normal (Table I) The alkaline phosphatase value remained slightly increased IgG IgA and IgM were within normal limits both before and during treatment Measurements of the hilar and pulmonary infiltrations revealed a decrease in size (Table II) The largest peripheral lymph node had softened considerably but remained about 1 cm in diameter

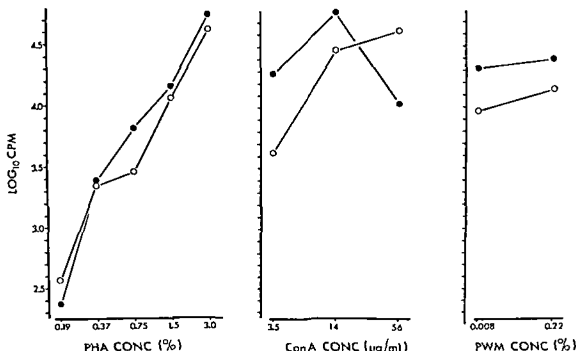


Fig 1 Absolute ^{14}C thymidine uptakes in cultures of lymphocytes from the patient (○—○) and the control (●—●) containing various concentrations of mitogen These tests were performed before the start of interferon therapy

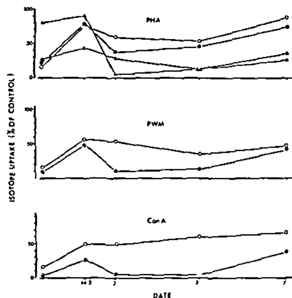


Fig 2 Relative stimulations of the patient s lymphocytes by mitogens in vitro The first test was conducted on Jan 11 1974 and the last on Jan 7 1975 The lymphocytes were tested before (Jan 11) and during (March 14 and April 29) interferon treatment and before (Aug 26 1974) and during (Jan 7 1975) CVPP treatment *Top* response of the cells to various concentrations of PHA 3% (O—O) 1 5% (●—●) 0 75% (Δ—Δ) 0 37% (▲—▲) *Middle* response of the cells to PWM 0 22% (O—O) 0 008% (●—●) *Bottom* response of the cells to ConA 14 μg/ml (O—O) 3 5 μg/ml (●—●)

By this time there had been an evident improvement in the clinical picture but from now on regression was very The daily interferon dose was then raised to 7×10⁶ U Frequent examinations during the following months to reveal any further decrease in lymph node size ration biopsy from a superficial lymph node showed an increased number of Reed Sternberg cells and in Aug 1974 a peripheral gland was excised The histological picture was now one of a border case between LP and mixed cellularity At the same time clinical progression was evident with enlargement of superficial and hilar lymph nodes increasing pulmonary infiltrations and reappearance of pruritus Laboratory tests revealed an increase in haptoglobin and a slight rise in WBC (Tables I and II)

Anti interferon antibodies could not be detected in the patient s serum However owing to clinical progression interferon treatment was abandoned The patient had then received totally 1 377 mill U interferon during 7 months Instead the patient was given combined cytostatic treatment with CVPP In Jan 1975 the largest superficial node had again decreased to less than 1 cm in diameter the pulmonary infiltrations and enlargement of the hilar nodes had disappeared ESR and WBC had normalized and the haptoglobin value had decreased (Tables I and II)

Before during and after interferon therapy the blood lymphocytes were examined for their relative response to various mitogens in vitro Fig 1 shows the absolute stimulations of the cells from the patient and the control before interferon therapy was started (Jan 1974) As expected ¹⁴C thymidine uptake increased in linear fashion with increasing concentration of PHA An optimal ConA response was obtained with 14 μg/ml and the two concentrations of PWM employed produced about the same stimulation

Fig 2 compares the relative mitogen stimulation of the patient s lymphocytes before during and after interferon therapy and after treatment with cytostatic drugs for 4 months (Jan 1975) The figure shows that the response to all mitogens had increased 1½ months after interferon therapy was started After this time the response to the lowest concentrations of the mitogens decreased Treatment with three CVPP courses again resulted in enhanced relative mitogen responsiveness of the lymphocytes The lymphocyte population was also tested for its reactivity to PPD (0 1–100 μg/ml) In March 1974 the cells were weakly positive (1 100 cpm using 10 μg/ml) but on all other test occasions they were non reactive

DISCUSSION

Combination chemotherapy has considerably improved the prognosis for patients with disseminated Hodgkin s disease (8 14) For stage IV patients the remission rate is 80% when MOPP or MVPP treatment is employed (7 9) The mean 5 year survival rate is around 40% survival being about 10% better in the histological types known as lymphocyte predominance and nodular sclerosis (9) The combined cytostatic courses generally employed are too noxious to be regarded as satisfactory (14) although many patients tolerate them Hence there is a need for new and effective therapeutic agents with less deleterious side effects

The observations made here suggest that interferon is able to improve the clinical picture of Hodgkin s disease Soon after the initiation of therapy the patient started to gain weight his weakness and pruritus disappeared pathologically enlarged lymph nodes decreased in size and with the exception of serum alkaline phosphatase all laboratory tests gave normal values The clinical improvement was associated with an increased mitogenic responsiveness as shown by testing populations of peripheral lymphocytes from the patient However after 1½ months of treatment the rate of improvement slowed down and a stationary phase of about 4 months was followed by clinical progression of the disease Combined cytostatic courses were then given and so far partial remission has been ob-

tained The latter remission was again accompanied by enhanced mitogenic responsiveness of the patient s lymphocyte population

The mechanism(s) underlying the well documented anti tumour effect of interferon preparations in experimental animals is (are) still poorly understood (11) Interferon preparations have been shown to affect the animal s immune system exert cytostatic effects and inhibit the growth of oncogenic viruses (10) In vitro at the serum concentrations achieved in humans (5) with the treatment schedule described in this communication interferon inhibited the growth of certain lymphoma cell lines completely although other lines were unaffected (1) The symptoms of Hodgkin s disease remain unexplained and it is not known whether the B symptoms are due to tumour cell progression or concurrent infection Hence it is of interest that on administration of interferon all signs of the disease both clinical and as seen in laboratory tests diminished This finding was further substantiated by an increased mitogenic response of the patient s lymphocytes a response which has been used as an index of the stage of the disease (3)

During the course of the interferon therapy progression was again observed At that time the histological picture was definitely more histocytic with an increased number of Reed Sternberg cells The reason for the ultimate failure of the interferon treatment is completely unknown It is difficult to generalize from observations in a single patient Unfortunately higher doses could not be given and more patients could not be studied because of lack of interferon Anti interferon antibodies could not be demonstrated in the serum of the patient Progression probably resulted either from resistance of the tumour cells to interferon a phenomenon which has been described for mouse lymphoma (11) or/and from failure of some system of the body s defence affected by the interferon therapy To decide between these possibilities it would be highly desirable to be able to grow cells from patients with Hodgkin s disease in nude mice (mice with congenital absence of thymus thus having a reduced cell mediated immunity) and do model experiments Meanwhile since the interferon schedule described in this communication is devoid of the side effects commonly observed with combined cytostatic treatment interferon therapy could be added to protocols in pilot studies aimed at determining the possible applications of exogenous interferon in future clinical trials employing combinations of therapeutic agents

ACKNOWLEDGEMENT

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Light Chain Myeloma with Features of the Adult Fanconi Syndrome Six Years Remission Following one Course of Melphalan

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ABSTRACT A 41 year old woman presenting with renal failure, renal glucosuria and moderate anemia was found to have light chain myeloma indicated by a kappa chain M component in the serum heavy urinary excretion of kappa chains and plasma cell infiltration of the bone marrow After administration of one course of melphalan resulting in transient pancytopenia, the light chains disappeared completely, renal function returned to normal, glucosuria disappeared and the Hb concentration normalized During an observation period of six years she has remained in good health and there has been no sign of relapse

The introduction of chemotherapy in the treatment of multiple myeloma has resulted in substantial symptomatic improvement and a prolonged survival This applies especially to the category of patients classified as good risk i e satisfying criteria indicating absence of renal failure hypercalcemia infection granulocytopenia and thrombocytopenia and with an estimated survival time of more than two months (1)

Among the variables known to be directly related to the abnormal clonal proliferation of plasma cells the presence of light chains (Bence Jones protein) is the one closest associated with the pathogenesis of renal failure It can therefore be regarded as a sensitive marker of disease as well as an indication of a serious prognosis The excess production of light chains in multiple myeloma is also etiologically implicated in a number of other metabolic disturbances e g amyloidosis hypercalcemia and renal tubular transport defects such as the adult Fanconi syndrome

The case described in this report is uncommon perhaps unique in that the presenting symptoms were indicative of bad risk —leucopenia renal failure pronounced production of light chains which seemingly were related to renal glucosuria In spite of these prognostically ominous findings one course of melphalan resulted in the disappearance of all signs of multiple myeloma including the renal glucosuria a response that has lasted throughout an observation period of six years

CASE REPORT

The patient a woman born in 1927 was first seen in the Department of Medicine in 1967 for evaluation of goiter Apart from some minor gynecological disorders her earlier history was negative She was considered euthyroid The thyroid gland was slightly enlarged The remaining physical examination was negative The PBI was normal Hb 12 5 g/100 ml ESR 10 mm/hour There was no albuminuria or glucosuria

In April 1969 she began noticing tiredness thirst and polyuria of moderate degree At the end of May she was investigated in the Department of Surgery for diffuse cramplike abdominal pains No surgically amenable disease could be found but the presence of elevated ESR anemia proteinuria and glucosuria raised the suspicion of diabetes mellitus and she was referred to the Department of Medicine

She denied skeletal pains and infection proneness A moderate goiter could be palpated the rest of the physical examination was negative (Fig 1) The Hb was 10 2 g/100 ml RBC 3 4 mill /mm³ WBC 1 800/mm³ with 35% lymphocytes 4% monocytes 4% eosinophilic granulocytes 54% segment formed and 3% band formed

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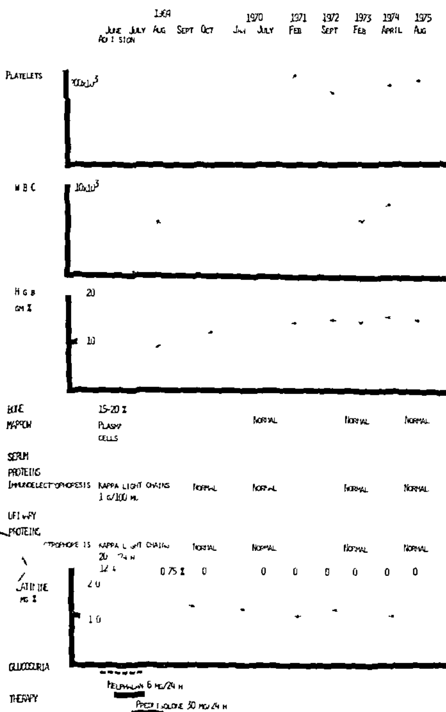


Fig 1 Clinical and laboratory data throughout the study

neutrophil granulocytes The platelet count was 180000/mm³ ESR 67 mm/hour

The urine was persistently alkaline during her five week stay in the hospital The 24-hour urine volume varied around 2500 ml the osmolality in the morning urine about 380 mOsm/kg The degree of proteinuria was of a magnitude of 10-3‰ (Esbach) The sediment was normal Trace amounts of glucose were present in the urine The fasting blood sugar and the glucose tolerance curve were normal but glucose was present in all urine specimens Serum creatinine was 1 5 mg/100 ml reaching a peak of 1 9 mg/100 ml on the 17th day of her hospital stay Creatinine clearance disclosed a reduced glomerular filtration rate of 54 ml/min Serum uric acid was 2 2 mg/100 ml Repeated serum estimations of calcium sodium potassium and standard bicarbonate were within normal limits Normal values were also obtained for serum cholesterol S-GOT S-GPT and alkaline phosphatases

Filter paper electrophoresis of serum was considered normal but the same procedure applied to the urine revealed a monoclonal peak with β mobility Quantitative immunoelectrophoresis of the serum (performed in the Department of Clinical Chemistry General Hospital Malmo) showed an M-component in the β 1 region consisting of kappa light chains in a concentration of 1 0 g/100 ml Other serum proteins of relevance were as follows albumin 4 4 IgG 1 2 IgA 0 32 and IgM 0 04 g/100 ml Immunoelectrophoretic analysis of the urine disclosed monoclonal kappa chains in a concentration of 1 0 g/100 ml The bone marrow had normal cellularity There were *15-20%* plasma cells *many of them atypical and multi*nucleated X rays of the skull thorax spine and pelvis were interpreted as normal

Therapy with melphalan was started and a total dose of 90 mg was administered during a period of 14 days The treatment resulted in severe bone marrow depression with granulocytopenia and thrombocytopenia reaching nadir values of 380 and 12000/mm³ respectively The administration of prednisolone resulted in normalization within one month

Frequent reinvestigations were undertaken during the ensuing six months No Bence Jones protein could be demonstrated in the urine with the heat acid precipitation test Albuminuria and glucosuria disappeared simultaneously within six weeks after the course of melphalan Within three months serum creatinine was within normal limits and within five months Hb ESR WBC and platelet count had returned to normal In a repeat immunoelectrophoresis in Oct 1969 no M-component could be detected in the serum or the urine only slight tubular proteinuria The patient has since been reinvestigated twice yearly for six years She has been in excellent health Repeat examinations of serum and urine immunoelectrophoresis have yielded normal results as have examinations of kidney function Hb peripheral blood counts and bone marrow

COMMENTS

Does this patient really represent a case of multiple myeloma? Differentiating multiple myeloma especially early myeloma from other conditions notably benign monoclonal gammapathy is a well recognized diagnostic problem As stated by Waldenstrom it is virtually impossible in an individual patient to tell if early myeloma is present or not (10) Regarding the criteria of manifestly malignant forms several authors express consonant views M-component exceeding 2 g/100 ml Bence Jones proteinuria reduction of normal immunoglobulins plasma cell percentage exceeding 10 anemia hypoalbuminemia and typical radiological findings are all signs indicative of multiple myeloma and are not consistent with the diagnosis of benign monoclonal gammapathy (4 5 10)

Some of these criteria are clearly not fulfilled by the present patient Thus she had normal concentrations of immunoglobulins lacked hypoalbuminemia and showed no roentgenologically detectable skeletal abnormalities However these factors are of subordinate diagnostic importance relative to the pronounced degree of Bence Jones proteinemia and proteinuria with which she presented The fact that she had a kappa light chain concentration in the serum of 1 g/100 ml and a urinary excretion corresponding to 1 g/100 ml is decidedly in favor of the diagnosis of malignancy *In the study by Dam*macco and Waldenstrom (3) of 42 subjects with benign monoclonal gammapathy the Bence Jones proteinuria never exceeded 6 mg/100 ml Hobbs in his study (4) of 304 patients with M components sets the limit even lower stating that Bence Jones proteinuria in excess of 1 mg/100 ml is of sinister significance

Excess production of light chains implies a higher degree of dedifferentiation of plasma cells than the manufacture of complete M components (4) Hence it signifies malignancy less equivocally Early detection by chance may explain the absence of lytic bone changes and the lack of depression of albumin and immunoglobulin synthesizing capacity in the present case An entity called idiopathic Bence Jones proteinuria was described by Kyle et al in 1973 (6) They reported two patients with monoclonal proteins type IgG K in the serum and excretion of kappa light chains in the urine approximating 1 g daily for more than seven years without the development of renal failure or other abnormalities associated with multiple myeloma However the fact that both these patients had monoclonal IgG serum components indicates a certain degree of balance in chain synthesis in contrast to the anarchic state of M protein synthesis exhibited by patients with light chain myeloma

It thus seems reasonable to conclude that the present patient had a light myeloma presenting with renal failure In a recent clinical study of 35 patients with light chain myeloma Stone and Frenkel (8) distinguish varying clinical manifestations of the disease spectrum manifestations masquerading as idiopathic renal failure solitary tumors of bone and amyloidosis Half the patients were azotemic when first seen and the renal damage was a major factor in the death of nine patients In agreement with Waldenstrom (10) they stress the multifactoral genesis of myeloma renal failure and they also regard the Bence Jones protein as the

main responsible agent interfering with diverse tubular functions

In this context it may be of interest to discuss the finding of glucosuria Glucose loading revealed its renal cause The patient was not investigated with respect to other components in the Fanconi syndrome i e aminoaciduria hypophosphatemia and hyperphosphaturia Apart from renal glucosuria there are however some other hints of tubular damage in the present case moderate urine concentration inability persistent production of alkaline urine tubular proteinuria and hypouricemia The latter finding is suggestive of a tubular transport defect as high values of the serum uric acid should be expected in the presence of renal failure and in relation to the increased turnover of nucleic acids associated with hematological malignancies

A small number of patients with multiple myeloma and the adult Fanconi syndrome have been reported The most thoroughly investigated is perhaps the case described by Lee et al (7) Their patient had kappa light chain disease deposition of crystals resembling myeloma protein in the proximal tubular cells hypophosphatemia with osteomalacia hypochloremic acidosis with inappropriatealy alkaline urine hypokalemia aminoaciduria hypouricemia and renal glucosuria No mention is made whether treatment of the myeloma affected the signs of the tubular transport defects An interesting feature of the present patient is the disappearance of glucosuria parallel with the dis arance of all other signs of multiple myeloma

e long remission in this patient after one urse of melphalan is exceptional and it has not been possible to find any comparable case in the literature All authors within this field tend to underscore the diagnostic as well as the serious prognostic significance of Bence Jones proteinuria Occasional patients showing transient disappearance of the Bence Jones protein during treatment with melphalan are mentioned (10) One patient with light chain myeloma living for 15 years after the diagnosis is reported by Hobbs (4) who however does not indicate if there was a remission or not These patients succumbed following relapse of disease and in general even short remissions are rare In most reported series patients with light chain myeloma have a short median survival e g 19 months in the study by Stone and Frenkel (8) for patients without and 7 months for patients with amyloidosis

The present patient fulfilled two criteria said to indicate bad risk i e renal failure and granulocytopenia Still she responded to one course of melphalan with complete disappearance of all signs indicative of light chain myeloma Her transient but severe pancytopenia may be of relevance in this context Admittedly the dosage was probably too high in relation to her renal insufficiency On the other hand transient pancytopenia has been claimed to be characteristic for patients responding to therapy while it is rare in those not responding (1) However early detection of the disease by chance and the patient being a good responder cannot be the sole explanations for the therapeutic success

Sullivan and Salmon (9) have studied the kinetics of myeloma cell growth and regression by calculating the synthetic rate of the M-component and the total body tumor cell number Tumor growth and drug induced tumor regression were found to follow kinetic laws showing evidence of the same retardation effect during growth and regression During the period of growth the proliferating fraction of the tumor decreased while it increased during regression During treatment with alkylating agents a plateau is reached representing a balance between drug induced cell death and increased tumor cell birth resulting from the expanding proliferative fraction A reciprocal feedback inhibition seems to be operating the myeloma cells depressing the normal population of plasma cells—thus inhibiting synthesis of normal immunoglobulins—and vice versa Could it be that the normal plasma cell population in the present patient after completed therapy was able to suppress the remnants of her malignant clone? The question is speculative but the hopeful fact remains that even seemingly highly malignant disease can be brought into remission in cooperation with the benevolent but unpredictable forces which for lack of detailed knowledge might be called Nature

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Sheehan's Syndrome of Hypothalamic Origin in a Woman with Juvenile Diabetes Mellitus

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ABSTRACT A 25-year-old woman with severe diabetes mellitus since the age of 7 developed anterior pituitary insufficiency after pregnancy toxaemia with hypofunction of the thyroid, ovaries and adrenal cortex Following the development of Sheehan s syndrome, her insulin requirement decreased dramatically I v administration of TRH, LRH and vasopressin induced nearly normal pituitary response levels of TSH, LH *and plasma cortisol Indicating a* hypothalamic damage as the primary aetiological factor

Before the detection of the hypothalamic releasing factors it was impossible to establish an exact differential diagnosis between hypothalamic lesions and pituitary damage There has been a considerable number of publications about panhypopituitary states caused by infarction and necrosis of the anterior pituitary (5) A special entity of panhypopituitarism has been described by Sheehan et al in a series of communications (8 9 10) The cause of the panhypopituitarism in these cases is believed to be sudden anterior pituitary necrosis due to clinical shock or excessive loss of blood in connection with delivery Since a large number of cases with clinical Sheehan s syndrome never reach autopsy the possibility of hypothalamic damage as the essential primary factor in the pathogenesis of the syndrome in some cases cannot be excluded It has recently been demonstrated that hypopituitarism may have a hypothalamic origin after irradiation (6) and following a traumatic damage to the hypothalamus (12)

In order to find out whether primary hypothalamic damage could be the causative factor in the development of post partum hypopituitarism an attempt was made to stimulate the pituitary by hypothalamic releasing factors in a patient who developed a clinically typical Sheeh[illegible] after a pregnancy toxicosis The case [illegible] lar interest, as the patient had severe j[illegible] betes which was considerably ameliorated after the development of the hypopituitary state (the Houssay phenomenon) The patient is thus a close parallel to the famous case of Poulsen (7)

CASE REPORT

The patient was a 25 year-old woman Her grandmother had diabetes mellitus and her mother had been operated on for thyreotoxicosis The patient developed diabetes mellitus at the age of 7 after a bacterial infection The diabetes was considered brittle during the first years and she required about 100 IU insulin daily Menarche occurred at 12 and thereafter she had normal regular menstruations Apart from three episodes of urinary tract infections she had been otherwise well

The patient became pregnant at 23 years of age During pregnancy she increased in weight from 56 to 69 kg In the 7th month of pregnancy she suddenly developed a pregnancy toxicosis and was delivered by Ceasarean section two months before full term The child developed cerebral palsy probably because of perinatal cerebral damage At Caesarean section the patient lost about 600 ml blood and following delivery her weight returned to 58 kg She exhibited frequent hypoglycaemic attacks and her insulin requirement fell from 100 to about 30 IU/day

After delivery the patient developed total amenorrhoea muscular weakness loss of libido loss of axillary and pubic hair The skin became pale and dry and the patient became extremely sensitive to cold Further clinical symptoms were a puffy face and oedematous legs psychic indifference some loss of memory scanty eyebrows depigmented nipple areolae decreased pulse rate and a low BP Two years after delivery she was admitted to our department for endocrinologic investigation In the mean time she had been treated with low doses of cortisone and thyroxine

Clinical examination on admission revealed signs of hypothyroidism and absence of the secondary sex characters Gynecological examination revealed a narrow, dry

Table I *Some endocrine laboratory data before and during combined hormone substitution therapy*

	On admission	After 3 months on hormone substitution[b]
Urinary 17 ketosteroids (mg/24 h)	2 2	2 8
Urinary 17 hydroxycorticoids (mg/24 h)	1 9	9 2
Urinary total oestrogens (μg/24 h)	2 0	6 2
Urinary progesteron (ng/ml)	<1 0	
Serum PBI (μg/100 ml)	2 6	6 5–9 2
In vitro T_3 uptake test (%)	53	85
Serum FSH (ng/ml)	2 0	1 0
Serum LH (ng/ml)	0 8	1 0
Serum growth hormone (ng/ml)	<0 3	
Plasma cortisol (μg/100 ml)	9 8 10 9 9 2	17 6 19 0 15 4
at 04 08 12 a m 04 08 12 p m	11 7 9 1 6 5	49 8 44 0 25 9
Serum cholesterol (mg/100 ml)	345	319
Serum triglycerides (mmol/l)	2 8	2 0

[a] No hormone substitution except Insulin Novo Semilente® 12 IU and Insulin Novo Lente® 12 IU daily
[b] Ethinyl oestradiol (50 μg×2) norethisterone acetate (5 mg×1) hydrocortisone acetate (10 mg×2) l thyroxine (0 15 mg×1) Insulin Novo Lente (8 IU) Insulin Novo Semilente (8 IU)

vagina and a small atrophied uterus ECG showed sinus bradycardia and low voltage X ray of the skull showed normal anatomy Table I shows the results of relevant laboratory investigations As will be seen the 17 ketosteroids 17 hydroxycorticoids BPI T_3 resin test and urinary oestrogens all showed low values Thus the clinical signs and the laboratory findings agree perfectly with the classical picture of anterior pituitary insufficiency

In order to find out whether the patient s pituitary cells were responsive to hypothalamic stimuli three different kinds of releasing factor tests were performed with TRH LRH and vasopressin respectively The results are shown in Table II It is apparent that TRH in two experiments induced a significant TSH response from the tary Likewise the LH levels increased significantly LRH stimulation Vasopressin is thought to stimulate ACTH production through CRF release A vasopressin infusion in two experiments significantly increased the plasma cortisol levels The experiments demonstrated that the pituitary cells responded rapidly to stimulation by releasing factors Hence it can be concluded that despite a clinically manifest hypopituitarism the anterior pituitary was responsive and thus could not have been destroyed by necrosis This means that the primary lesion in this case must be sought at a higher level probably in the hypothalamus

When the investigations had been completed substitution therapy was started The final drug regime was as follows Insulin Novo Lente® 8 IU+Insulin Novo Semilente® 8 IU in the morning hydrocortisone acetate 10 mg×2 daily l thyroxine 0 15 mg daily ethinyl-oestradiol 50 μg×2 daily for three weeks followed by one week s

Table II *Effect of TRH LRH and vasopressin on the TSH LH and plasma cortisol levels*

All experiments made during the investigation period before substitution therapy Drugs were injected i v at zero time

		Time (min)								
		−10	0	10	20	30	40	60	80	120
TRH (200 μg)	Serum TSH (μU/ml)									
	Exp 1		9 5	24	25		14			
	Exp 2	7 3	9 0	16	19		14			8 2
LRH (100 μg)	Serum LH (ng/ml)		0 7	0 9	1 9	1 5	1 8	2 9	1 3	1 5
			Time (h)							
Vasopressin (10 IU)	Plasma cortisol (μg/100 ml)		0	2	5					
	Exp 1		10 0	27 8	15 2					
	Exp 2		11 5	21 6	17 4					

break norethisterone acetate 5 mg daily during the third week on oestrogen On this regimen the patient rapidly became practically symptom free The secondary sex characters reappeared and she started to menstruate regularly The size of the uterus and vagina normalized and the patient could resume normal sexual life Three months after the onset of the substitution the laboratory values were essentially normal (Table I) Two years later the patient is feeling well and has no signs of pituitary insufficiency

DISCUSSION

There are several factors which predispose to the development of anterior pituitary insufficiency In the classical case reported by Simmonds (11) a septic embolus was probably the cause Peri partum pregnancy complications such as severe blood loss or hypovolaemic shock have been shown to be important precipitating factors (8 10) According to these authors the enlargement of the pituitary gland with increased circulatory requirements during pregnancy makes the gland exceptionally vulnerable to ischaemic lesions Infarction of the pituitary in patients with diabetes mellitus may also be more common than in a healthy subject (1, 4) The present case is interesting since both the patient s diabetic state and her pregnancy toxaemia probably contributed to the development of the panhypopituitarism In connection with the Caesarean section this patient neither lost large amounts of blood nor exhibited clinical signs of shock However the pregnancy toxaemia may have caused a local vasospasm around the hypothalamus hypophyseal region resulting in the anterior pituitary insufficiency Transient occlusive spasm of the vessels supplying the area around the pituitary gland has been postulated to be of aetiological significance (2 10)

That stimulation of the pituitary by hypothalamic releasing factors resulted in significant elevation of TSH LH and plasma cortisol levels was an unexpected finding in the present case This means that the secretory capacity of the cells of the anterior pituitary must be intact In numerous classical cases of Sheehan s syndrome pituitary necrosis has been demonstrated at autopsy In a recent publication of three cases (3) the plasma TSH response to TRH was totally absent However many cases with Sheehan s syndrome have only been observed in living women thus without any autopsy verification of the diagnosis

Our results demonstrate that a hypothalamic form of post partum pituitary insufficiency must be accepted as a reality Secondary hypopituitarism due to hypothalamic insufficiency has recently been described by Woolf and Schalch (12) after basilar skull fracture and by Larkins and Martin (6) after irradiation of the hypothalamus At present the treatment of hypopituitarism will be the same notwithstanding the anatomical differences i e combined substitution with different target organ hormones However development of long acting hypothalamic releasing factor preparations will probably soon permit a new type of more causal treatment and this may make a distinct aetiological diagnosis important

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Acute Myeloma

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.BSTRACT This patient had an acute onset of ıyeloma, with hypercalcemia, a high M-component ı the plasma, Bence Jones proteinuria and 37% lasma cells in the bone marrow sample After mel halan treatment (210 mg totally) he seems to have a omplete cure, with total disappearance of the 1-component Bence Jones proteinuria myeloma ells, hypercalcemia and elevated ESR for almost hree years

\lthough the prognosis in multiple myeloma is un avorable a very prolonged course has been re orted in a few cases (1 2 3 4) However a com lete cure induced by cytotoxic drugs has never een reported before

CASE REPORT

ι 76-year-old man was admitted to the hospital in March 973 For a few weeks his gait had been unsteady he had ost appetite and had large urine volumes He had no ains He had had duodenal ulcer bleedings twice in 1969 nd in 1971 he developed cardiac decompensation which vas treated with digitalis and diuretics After a few nonths he had two attacks of gout and has ever since been reated with allupurinol 100 mg b d His ESR was consid rably increased (84 mm) during the gout attacks but be ore and after it was normal 22 mm in June and 34 mm in Dec 1972 His serum calcium was normal 4 7 mEq/l and Hb 15 2 g/100 ml

On admission the patient was slightly confused His BP was 190/90 and heart rate 84 regular Serum calcium was igh 7 0 mEq/l serum creatinine was 4 5 mg/100 ml ESR 97 mm and Hb 11 2 g/100 ml Bone marrow from a sternal puncture showed 37% plasma cells Plasma protein electrophoresis showed a monoclonal IgGK component 7 6 g/100 ml with a marked reduction of the other immunoglobulins and of albumin (2 9 g/100 ml) In the urine a Bence Jones protein (K) was found (350 mg/l) X ray of the skull spine and pelvis did not reveal any visible local destruction

The patient was treated with accelerated diuresis (Hb falling to a minimum of 8 9 g/100 ml) and with melphalan 5 mg daily for 20 days and he also had steroids for a week during which serum calcium fell from 7 1 to 3 9 mEq/l His general condition improved rapidly and he was able to leave the hospital after a month Sixteen days later a herpes zoster was diagnosed A few weeks later routine blood tests including plasma electrophoresis were performed in the Outpatient Clinic His serum calcium was still normal 4 9 mEq/l serum creatinine 1 4 mg/100 ml Hb 11 8 g/100 ml ESR 94 mm and the platelet and white cell counts were again normalized after the mel phalan induced depression A maintenance dose of 2 mg melphalan daily was then started

Soon afterwards the result of the electrophoresis ar rived but had to be rechecked because of the profound changes Now the monoclonal component had completely disappeared in the γ 1 zone but in the γ 2 3-zone there was a marked increase of IgG (2 8 g/100 ml) slowly de creasing to 1 8 g/100 ml within a month The Bence Jones proteinuria had completely disappeared and the mel phalan therapy was discontinued after a total dose of 210 mg The bone marrow now had only 1 8% plasma cells The eletrophoresis pattern has been checked repeatedly up to now (32 months after diagnosis of myeloma) and remains stable At the latest examination in Nov 1975 his ESR was 23 mm plasma IgG 1 5 IgA 0 25 and IgM 0 05 g/100 ml He has remained in good health clinically

DISCUSSION

The onset of this acute myeloma had evidently taken place shortly after the examination in Dec 1972 when the laboratory data were within the same ranges as in previous years Three months later the patient had a fulminant picture of hypercalcemia and further examination revealed that myeloma cells accounted for more than one third of the bone marrow cells A very high M-component with con comitant depression of the other immunoglobulins and albumin was found in the plasma Bence Jones protein was found in the urine and the renal func tion was seriously impaired

The very rapid proliferation of myeloma cells occurring within weeks or a few months at most is more like the explosive cell proliferation seen in acute leukemia than in most myeloma cases This extremely rapid clinical development stands out distinctly but even more surprising is the complete and rapid cure Almost three years later the patient is doing excellently and shows no signs of myeloma The melphalan therapy given is believed to be the treatment of choice but still its main advantages are confined to pain relief and prolongation of life for some years It is possible and even likely that the immense proliferation of myeloma cells was unusually sensitive to melphalan Shortly after the initial therapy the patient developed herpes zoster which might indicate profound changes in immunity possibly secondary to the effect of therapy Except for the zoster, the patient has had an uneventful recovery

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